1. General Information

ID 136-53-8

Date December 06, 2004

201-16426B

1.0 SUBSTANCE INFORMATION

Generic Name	:	Hexanoic acid, 2-ethyl, zinc salt
Chemical Name	:	Hexanoic acid, 2-ethyl, zinc salt
CAS Registry No.	:	136-53-8
Component CAS Nos.	:	
EINECS No.	:	205-251-1
Structural Formula	:	$C_{16}H_{30}O_4Zn$
Molecular Weight	:	351.8006
Synonyms and Trade names	:	Zinc 2-ethylhexanoate; ethylhexanoic acid zinc salt; Therm-Chek
References	:	http://www.chemfinder.com

2.1 MELTING POINT

Type	:	Melting Point/Melting Range
Guideline/method	:	OECD No. 102 EEC Directive 92/69, A.1 EPA OPPTS Guideline 830.7100
Value	:	-47 °C±1°C
Decomposition	:	
Sublimation	:	
Year	:	2003
GLP	:	Yes
Test substance	:	Hexanoic Acid, 2-Ethylhexyl, Zinc salt, 99%
Method	:	Combination of thermal analysis using a calorimeter and visual test for physical state change
Method detail	:	
Result	:	The freezing temperature for Hexanoic Acid, 2-Ethylhexyl, Zinc salt was determined to be -47 °C±1°C
Remark	:	Testing was conducted on triplicate samples
Reliability	:	(1) Reliable without restrictions
Reference	:	Determination of the Melting Point/Melting Range of Hexanoic Acid, 2-Ethylhexyl, Zinc salt RCC Study Number 849075, RCC, Ltd., Itingen, Switzerland, August 21, 2003.

2.2 BOILING POINT

Type	:	Boiling Point/Boiling Range
Guideline/method	:	OECD No. 103 EEC Directive92/69, A.2. EPA OPPTS Guideline 830.7220
Value	:	> 400 °C
Decomposition	:	
Year	:	2003
GLP	:	Yes
Test substance	:	Hexanoic Acid, 2-Ethylhexyl, Zinc salt, 99%
Method	:	Combination of thermal analysis using a calorimeter and visual test for physical state change and weight change.
Method detail	:	
Result	:	In the temperature range of 25 to 400°C, no boiling activity (endothemic peaks using thermal analysis) could be observed.
Remark	:	The absence of a boiling point or range at these temperatures was confirmed in a duplicate experiment.
Reliability	:	(1) Reliable without restrictions
Reference	:	Determination of the Boiling Point/Boiling Range of Hexanoic Acid, 2-Ethylhexyl, Zinc salt RCC Study Number 849076, RCC, Ltd., Itingen, Switzerland, August 21, 2003.

2.3 DENSITY

Type	:	Not stated
Guideline/method	:	Not stated

Value	:	1.180
Year	:	Not stated
GLP	:	No
Test substance	:	Hexanoic Acid, 2-Ethylhexyl, Zinc salt, 99%
Method	:	Not stated
Method detail	:	
Result	:	The density of Hexanoic Acid, 2-Ethylhexyl, Zinc salt, is reported to be 1.180
Remark	:	
Reliability	:	(2) Reliable with restrictions
Reference		MSDS dated December, 2003

2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	Other: calculated
Value	:	1.59E-006 mm Hg
Decomposition	:	
Year	:	2006
GLP	:	No
Test substance	:	SMILES : [Zn](OC(=O)C(CC)CCCC)OC(=O)C(CC)CCCC CHEM : Zinc 2-ethylhexanaote CAS NUM: 000136-53-8 MOL FOR: C16 H30 O4 Zn1 MOL WT : 351.81
Method	:	MPBPWIN (v1.41)
Method detail	:	
Result	:	Vapor Pressure Estimations (25 deg C): (Using BP: 429.37 deg C (estimated)) (MP not used for liquids) VP: 1.83E-007 mm Hg (Antoine Method) VP: 1.59E-006 mm Hg (Modified Grain Method) VP: 3.32E-006 mm Hg (Mackay Method) Selected VP: 1.59E-006 mm Hg (Modified Grain Method)
Remark	:	Zinc hexanoate readily dissociates at neutral pH
Reliability	:	(2) valid with restrictions
Reference	:	EPIWIN SUMMARY (v3.11)

2.5 PARTITION CONSTANT

Type	:	Octanol-water
Guideline/method	:	KOWWIN Program (v1.67)
Value	:	4.4688
pH value	:	
Year	:	2006
GLP	:	no

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Test substance	:	SMILES : [Zn](OC(=O)C(CC)CCCC)OC(=O)C(CC)CCCC CHEM : Zinc 2-ethylhexanaote MOL FOR: C16 H30 O4 Zn1 MOL WT : 351.81
Method	:	
Method detail	:	
Result	:	KOWWIN Program (v1.67) Results: Log Kow(version 1.67 estimate): 4.47 SMILES : [Zn](OC(=O)C(CC)CCCC)OC(=O)C(CC)CCCC CHEM : Zinc 2-ethylhexanaote MOL FOR: C16 H30 O4 Zn1 MOL WT : 351.81 TYPE | NUM | LOGKOW FRAGMENT DESCRIPTION | COEFF | VALUE Frag | 4 | -CH3 [aliphatic carbon] | 0.5473 | 2.1892 Frag | 8 | -CH2- [aliphatic carbon] | 0.4911 | 3.9288 Frag | 2 | -CH [aliphatic carbon] | 0.3614 | 0.7228 Frag | 2 | -C(=O)O [ester, aliphatic attach] |-0.9505 | -1.9010 Frag | 1 | Zinc [Zn] |-0.7000**| -0.7000 Const | | Equation Constant | | 0.2290 NOTE | | An estimated coefficient (**) used Log Kow = 4.4688
Remark	:	Zinc hexanoate readily dissociates at neutral pH
Reliability	:	(2) valid with restrictions
Reference	:	EPIWIN SUMMARY (v3.11)

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2.6.1 SOLUBILITY IN WATER

Type	:	Water solubility
Guideline/method	:	OECD No. 15 EEC Directive 92/69, A. 6. EPA OPPTS Guideline 830.7840
Value	:	20.2 mg/l @20ºC
pH value	:	6.6 to 7.2
concentration	:	
Temperature effects	:	20 ± 0.5ºC
Examine different pol.	:	
PKa	:	6.99 at 20°C
Description	:	
Stable	:	
Deg. product	:	
Year	:	2004
GLP	:	Yes
Test substance	:	Hexanoic Acid, 2-Ethylhexyl, Zinc salt, 99%
Deg. products CAS#	:	
Method	:	The column elution method was used to determine the saturation concentration of the test item in pure water at 20°C. Sampling of the column eluate was by atomic absorption specotroscopy.
Result	:	The water solubility of Hexanoic Acid, 2-Ethylhexyl, Zinc salt was 20.2 mg/l @20ºC based on a measured concentration of 3.76 mg Zn/l (±0.27mg Zn/l)
Remark	:	Twelve replicate elutions and analyses were conducted and all results

differed by less than 30%**.**

Reliability	:	(1) Reliable without restrictions
Reference	:	Determination of the Water Solubility of Hexanoic Acid, 2-Ethylhexyl, Zinc salt RCC Study Number 849078, RCC, Ltd., Itingen, Switzerland, July 21, 2004.

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	> 250 °F
Year	:	
GLP	:	
Test substance	:	Mixture of zinc 2-ethylhexanoate (98% by weight) and diethylene glycol monomethyl ether
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	MSDS dated 11/30/00, prepared by The Shepherd Chemical Company

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	AOP Program (v1.91)
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) epsilon (max) epsilon (295)
Conc. of substance	:	
DIRECT PHOTOLYSIS		
Half-life (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	
Rate constant	:	12.7363 E-12 cm3/molecule-sec
Degradation	:	50% after 10.078 hrs
Deg. product	:	2-ethylhexanoic acid Zinc salt
Year	:	
GLP	:	
Test substance	:	SMILES : [Zn](OC(=O)C(CC)CCCC)OC(=O)C(CC)CCCC CHEM : Zinc 2-ethylhexanaote MOL FOR: C16 H30 O4 Zn1 MOL WT : 351.81
Deg. products CAS#	:	
Method	:	AOP Program (v1.91
Method detail	:	
Result	:	AOP Program (v1.91) Results: SUMMARY (AOP v1.91): HYDROXYL RADICALS ---------- Hydrogen Abstraction = 12.7363 E-12 cm3/molecule-sec Reaction with N, S and -OH = 0.0000 E-12 cm3/molecule-sec Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec Addition to Aromatic Rings = 0.0000 E-12 cm3/molecule-sec Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec OVERALL OH Rate Constant = 12.7363 E-12 cm3/molecule-sec HALF-LIFE = 0.840 Days (12-hr day; 1.5E6 OH/cm3) HALF-LIFE = 10.078 Hrs ---------- SUMMARY (AOP v1.91): OZONE REACTION ---------- --- ****** NO OZONE REACTION ESTIMATION ****** (ONLY Olefins and Acetylenes are Estimated) Experimental Database: NO Structure Matches
Remark	:	Zinc hexanote readily dissociates at neutral pH
Reliability	:	(2) valid with restrictios
Reference	:	EPIWIN SUMMARY (v3.11)

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3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKa	:	6.99 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Zinc 2-ethylhexanoate, 1% ethylene glycol monomethyl ether, CAS number 136-53-8, lot number F05L03, received from Alfa Aesar Chemical Company. Liquid, purity of 22.39% zinc.
Approximate water solubility	:	100 mg/L as determined visually in preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water
Method detail	:	Three replicate samples of zinc 2-ethylhexanoate were prepared at a nominal concentration of 50 mg/L by fortification of degassed water (ASTM Type II) with a 10 mg/mL stock solution of the test substance in methanol. Each sample was titrated against 0.001N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result	:	Mean (N = 3) pKa value was 6.99 (SD = 0.0704) at 20°C
Remark	:	The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).
Reliability	:	[1] Reliable without restriction.
Reference	:	Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of zinc 2-ethylhexanoate, 1% ethylene glycol monomethyl ether, Wildlife International, Ltd. Study No. 534C-102, conducted for the Metal Carboxylates Coalition.

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3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	
Concentration	:	mg/l
Substance measured	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.3.1 TRANSPORT (FUGACITY)

Type	:	Level III Fugacity Model
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Year	:	2006
Test substance	:	Level III Fugacity Model (Full-Output):

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Chem Name : Zinc 2-ethylhexanaote
Molecular Wt: 351.81
Henry's LC : 1.05e-007 atm-m3/mole (calc VP/Wsol)
Vapor Press : 1.59e-006 mm Hg (Mpbpwin program)
Log Kow : 4.47 (Kowwin program)
Soil Koc : 1.21e+004 (calc by model)

Method : Level III Fugacity Model

Method detail :

Result : Level III Fugacity Model (Full-Output):

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	1.26	20.2	1000
Water	31	360	1000
Soil	62.3	360	1000
Sediment	5.49	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	6.22e-012	483	140	16.1	4.68
Water	5.07e-013	665	345	22.2	11.5
Soil	3.97e-014	1.34e+003	0	44.5	0
Sediment	1.57e-013	29.5	1.22	0.982	0.0408

Persistence Time: 372 hr
Reaction Time: 444 hr
Advection Time: 2.29e+003 hr
Percent Reacted: 83.8
Percent Advected: 16.2

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 20.16
Water: 360
Soil: 360
Sediment: 1440
Biowin estimate: 3.018 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Remark : Zinc hexanoate readily dissociates at neutral pH
Reliability : (2) valid with restrictions
Reference : EPIWIN SUMMARY (v3.11)

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to
Contact time :

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Degradation	:		(±)	% after		day(s)
Result	:					
Kinetic of test subst.	:	%	(specify time and % degradation)			
		%				
		%				
		%				
		%				
Control substance	:					
Kinetic	:	%				
		%				
Deg. product	:					
Year	:					
GLP	:					
Test substance	:					
Deg. products CAS#	:					
Method	:					
Method detail	:					
Result	:					
Remark	:					
Reliability	:					
Reference	:					

3.7 BIOCONCENTRATION

Type	:			
Guideline/method	:			
Species	:			
Exposure period	:		at	°C
Concentration	:			
BCF	:			
Elimination	:			
Year	:			
GLP	:			
Test substance	:			
Method	:			
Method detail	:			
Result	:			
Remark	:			
Reliability	:			
Reference	:			

4.1 ACUTE TOXICITY TO FISH

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
LC0	:	
LC50	:	
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Static
Guideline/method	:	OECD TG 202
Species	:	*Daphnia magna*
Exposure period	:	48 hrs
NOEC	:	6.2 mg/L
EC0	:	
EC50	:	14 mg/L
EC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	no
Analytical monitoring	:	yes
Year	:	2006
GLP	:	yes
Test substance	:	Zinc, 2-ethyl hexanoate (22% zinc)
Method	:	Following preliminary range-finding tests, twenty daphnids (2 replicates of 10 animals) were exposed to an aqueous solution of the test material at nominal concentrations of 0.70, 1.3, 2.2, 3.9, 7.0, 13, 22, 39 and 70 mg/l* for 48 hours at a temperature of 20.7°C to 21.4°C under static test conditions. The test material solutions were prepared by stirring an excess (100 mg/l) of test material in reconstituted water at approximately 1500 rpm at a temperature of 21°C for 24 hours prior to removing any undissolved test material by filtration (0.2 J.1III Sartorius Sartopore filter, first approximate 500 ml discarded in order to pre-condition the filter) to give a saturated solution with a nominal test concentration of 70 mg/l*. The number of immobilised Daphnia were recorded after 24 and 48 hours. The water solubility determined during this test was higher than the value

supplied by the Sponsor (20.2 mg/l). This was considered to be due to dissolved salts such as calcium and magnesium in the reconstituted water increasing the solubility of the test material.

A positive control conducted approximately every six months used potassium dichromate as the reference material. Daphnia magna was exposed to an aqueous solution of the reference material at concentrations of 0.32, 0.56, 1.0, 1.8 and 3.2 mg/l for 48 hours at a temperature of approximately 20°C under static test conditions. Immobilisation and any adverse reactions to exposure were recorded after 3, 24 and 48 hours.

Method detail :

Result : Analysis of the test preparations was conducted for zinc and hexanoate during the test and the results were calculated as the test material, zinc hexanoate. Analysis of the test preparations at 0 hours showed measured test concentrations of 0.516 to 62.9 mg/l as test material based on analysis for zinc and measured test concentrations of 0.561 to 86.0 mg/l as test material based on analysis of hexanoate.

Analysis of the test preparations sampled at 48 hours showed measured test concentrations of 0.411 to 59.3 mg/l as test material based on analysis for zinc and measured test concentrations of 1.20 to 75.3 mg/l as test material based on analysis of hexanoate. The lowest test concentration of showed a measured concentration of less than the limit of quantitation of the analytical method based on analysis of hexanoate.

All of the results showed an increase in measured test concentration with increasing nominal concentrations and the values based on analysis of hexanoate showed slightly higher measured values than those based on zinc analysis. For both zinc and hexanoate analyses, a slight decline was shown in the majority of the measured test concentrations over the 48 hours of the test.

Analysis of the samples for hexanoate involved several stages in its determination and each stage of this process may have caused losses or variability in the results. However, the zinc determination was a single stage digestion to release the zinc which was determined by voltametry. The zinc determination was considered to be the more accurate and reliable technique and therefore, the results of the test have been based on the measured concentrations of test material based on analysis for zinc. It was considered that the greater variability shown in the method for analysis for hexanoate compared to the more accurate method used for analysis of zinc may have been the reason for the differences shown in the measured concentrations from each method.

Given that a decline was shown in the measured test concentrations over 48 hours the results were based on the geometric mean measured concentrations of test material based on zinc analysis which were calculated to be 0.461, 1.08, 1.88,3.23,6.18,11.0,20.0,35.2 and 61.1 mg/l.

The 48-Hour ECso based on the geometric mean measured test concentrations of the test material based on zinc analysis was 14 mg/l with 95% confidence limits of 11 - 17 mg/l and the No Observed Effect Concentration was 6.2 mg/l.
The 48-Hour ECso for the reference material to Daphnia magna based on nominal concentrations was 0.97 mg/l with 95% confidence limits of 0.85 - 1.1 mg/l. The No Observed Effect Concentration was 0.56 mg/l.

Remark	:	
Reliability	:	(1) Valid without restriction
Reference	:	Safepharm Laboratories (2006) Zinc Hexanoate: ACUTE TOXICITY TO DAPHNIA MAGNA SPL Project NUMBER: 1683/015

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	:
Guideline/method	:
Species	:
Endpoint	:
Exposure period	:
NOEC	:
LOEC	:
EC0	:
EC10	:
EC50	:
Other	:
Other	:
Other	:
Limit test	:
Analytical monitoring	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st: 2nd: 3rd:
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

5.1.1 ACUTE ORAL TOXICITY

Type	:	Acute Oral (LD50) Toxicity
Guideline/Method	:	
Species	:	Rat
Strain	:	Sherman-Wistar albino
Sex	:	Male and female
Number of animals	:	10 per dose (5 male, 5 female)
Vehicle	:	
Doses	:	1.58, 2.0, 2.51, 3.16, 3.98, 5.01 and 6.32 g/kg
LD50	:	Males: 3.7 g/kg (95% CI: 3.04 – 4.62 g/kg). Females: 3.55 g/kg (95% CI: 2.95 – 4.26 g/kg)
Year	:	1980
GLP	:	Not reported
Test substance	:	Zinc octoate, 18%, Lot # 150. Described as zinc 2-ethylhexanoate 79.1%, mineral spirits 20.9% (CAS # 8032-32-4). Negligibly soluble in water, soluble in organic solvents. Density 1.022 g/mL.
Method	:	Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.3.
Method detail	:	Animals (200 - 300 g) fasted overnight (food only) prior to dosing, weighed and administered the test material (as received) via intragastric intubation.

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Observed for 14-days post-exposure.

Result : LD50 for Males: 3.7 g/kg (95% CI: 3.04 – 4.62 g/kg). LD50 for Females: 3.55 g/kg (95% CI: 2.95 - 42.6 g/kg). For males: 3/5, 4/5 and 5/5 rats died at the three highest doses, respectively. One rat died at 2.51 g/kg and one rat died at 3.16 g/kg. For females: 2/5, 3/5, 5/5, and 5/5 rats died at the four highest doses, respectively. For both sexes, within 1-2 hr following dosing, animals displayed numerous symptoms (slight ataxia, depression, ruffled, and drooling at lower doses; semi-comatose and death higher doses). Animals, which survived, recovered fully after 1-4 days. Gross necropsies were unremarkable.

Remark :

Reliability : [2] Reliable with restrictions. Basic data provided, exposure conditions not fully described. Comparable to guideline.

Reference : Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), study conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.1.2 ACUTE INHALATION TOXICITY

Type : Limit Test

Guideline/method :

Species : Rat

Strain : Albino

Sex : Male and female

Number of animals : 10 (5 male and 5 female)

Vehicle :

Doses : One concentration, 23.2 mg/L of a 25% w/v suspension in mineral spirits. Median particle diameter measured to ensure a respirable dose was received.

Exposure time : 1 hour

LC50 : > 23.2 mg/L (maximum attainable nominal concentration)

Year : 1980

GLP : Not reported

Test substance : Zinc octoate 18% (Lot # 150), prepared and used as a 25% w/v suspension in mineral spirits.

Method :

Method detail : Animals (205 – 210 g, average) were exposed to the test material inside a 260-L Plexiglas exposure chamber for 1 hour. Presumably whole body exposure, though not described in report. An aerosol was generated by a jet collision nebulizer; air was passed through the test material and into the chamber at 20 L/min., at 70ºF. Test material concentration was measured and determined to be 23.2 mg/L (determined by weighing the flask containing the aerosol before and after exposure). Particle size, determined for 5 minutes midway through the exposure period, was calculated to be 1.1 microns MMD (mass median diameter). Animals observed for 14 days post-exposure

Result : No mortality, no toxicity, and no adverse gross necropsy findings

Remark :

Reliability : [2] Reliable with restrictions. Basic data provided. Exposure conditions not described, duration of exposure and determination of measured test concentrations less than current guidelines require.

Reference : Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.1.3 ACUTE DERMAL TOXICITY

Type : Limit Test

Guideline/method :

Species	:	Rabbit
Strain	:	Albino
Sex	:	Male and female
Number of animals	:	Six (3 male and 3 female)
Vehicle	:	
Doses	:	One dose, 5 g/kg
LD50	:	> 5 g/kg
Year	:	1980
GLP	:	Not reported
Test substance	:	Zinc octoate, 18%, Lot # 150. Described as zinc 2-ethylhexanoate 79.1%, mineral spirits 20.9% (CAS # 8032-32-4). Negligibly soluble in water, soluble in organic solvents
Method	:	Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.40.
Method detail	:	Animals (2-3 kg) had their backs clipped free of hair and abraded 24 hours prior to dose administration. Each animal was weighed and the appropriate amount of test material applied to the back, covered with gauze and impervious damming. Dressings were removed after 24 hours, excess material removed, and backs wiped clean. Animals observed for 14 days post-exposure.
Result	:	No mortality or toxicity. No adverse gross necropsy findings
Remark	:	
Reliability	:	[2] Reliable with restrictions. Basic data provided. Exposure conditions not fully described, size of area of application not mentioned. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.2.1 SKIN IRRITATION

Type	:	Contact dermal irritation/sensitization
Guideline/method	:	
Species	:	Guinea pig, albino
Strain	:	
Sex	:	Male, weighing 300 – 400 g
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	10
Vehicle	:	
Classification	:	
Year	:	1980
GLP	:	Not reported
Test substance	:	Zinc octoate, 18%, Lot # 150.
Method	:	
Method detail	:	A 0.5 mL portion of material was applied to the intact skin test sites on the guinea pigs. A gauze patch was placed over the treated area and an impervious material was wrapped snugly around the trunks of the animals to hold the patch in place. After 24 hours, the patch was removed, the animals allowed to rest for 1 day, and another application was made to the same skin site. This sequence was repeated for a total of 10 applications, after which time the animals were given a two week rest period. Subsequently a challenge application was put on skin sites differing from the original test sites. The challenge application remained on for 24 hours. The sites were examined for irritation using the Draize method of scoring, 24 hours after each induction application and 24 and 48 hours after the challenge application.

Result	:	The test substance was a primary skin irritant and a fatiguing agent, but not a sensitizing agent.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.2.2 EYE IRRITATION

Type	:	Primary eye irritation
Guideline/method	:	
Species	:	Rabbits, young adults
Strain	:	Albino
Sex	:	
Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	Six
Vehicle	:	
Classification	:	
Year	:	1980
GLP	:	Not reported
Test substance	:	Zinc octoate, 18%, Lot # 150.
Method	:	
Method detail	:	0.1 mL of the test material was instilled into the right eyes of the animals while the other eye served as the untreated control. The test material was not washed from the eyes. The treated eyes were examined at 1, 2, 3, 5, and 7 days following exposure. Results were scored according to the Draize Scale of Scoring Ocular Lesions.
Result	:	The test substance was not a primary ocular irritant within the definition of the Federal Hazardous Substances Act.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.4 REPEATED DOSE TOXICITY

Type	:	7 day
Guideline/method	:	
Species	:	Rat
Strain	:	Sprague_Dawley
Sex	:	Male/female
Number of animals	:	30
Route of admin.	:	Oral (gavage)
Exposure period	:	7 days
Frequency of treatment	:	Daily
Post exposure period	:	None
Doses	:	150, 500 and 1000 mg/kg bw/d
Control group	:	Yes, concurrent vehicle
NOAEL	:	1000 mg/kg bw/d
LOAEL	:	
Other	:	
Year	:	2006
GLP	:	Yes
Test substance	:	
Method	:	The test material was administered by gavage to three groups, each of five

male and five female rats, for seven consecutive days, at dose levels of 150, 500 and 1000 mg/kg/day. A control group of five males and five females was dosed with vehicle alone (Arachis oil BP). Clinical signs, bodyweight development and food and water consumption were monitored during the study. Organ weight data was evaluated at the end of the study and all animals were subjected to a gross necropsy examination.

Method detail :

Result : Mortality. There were no mortalities throughout the treatment period. Clinical Observations. Increased salivation immediately post dose was observed for all females treated with 1000 and 500 mg/kg/day. Throughout the treatment period all males treated with 1000 mg/kg/day and males treated with 500 and 150 mg/kg/day also showed increased salivation immediately post dose. Bodyweight. No treatment-related effects were detected. Food Consumption. No treatment-related effects were detected. Water Consumption. No treatment-related effects were detected. Organ Weights. No treatment-related effects were detected. Necropsy. No treatment-related macroscopic findings were observed at post mortem examination.

Oral administration of Aluminium Stearate to rats, by gavage, at dose levels of 150, 500 and 1000 mg/kg/day for seven consecutive days resulted in a transient reduction in bodyweight gain for females treated with 1000 mg/kg/day. In the absence clinical signs of toxicity, this transient effect on bodyweight gain was considered not to have a detrimental effect on the health of the animals. The No Observed Adverse Effect Level (NOEL) was therefore considered to be 1000 mg/kg/day.

Remark :

Reliability : (1) valid without restrictions

Reference : Safepharm Laboratories (2006) ZINC HEXANOATE: SEVEN DAY REPEATED DOSE ORAL (GAVAGE) TOXICITY STUDY IN THE RAT

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Mutagenicity

Guideline/method :

System of testing : Ames assay, standard plate assay

Species : *Salmonella typhimurium*

Strain : TA98, TA100, TA1535, TA1537 and TA1538

Test concentrations : 1, 10, 100, 500, and 1000 µg/plate, in duplicate. Dissolved in ethanol.

Cytotoxic concentr. :

Metabolic activation : Conducted both with and without activation. S-9 fraction derived from rats induced with Aroclor 1254 per Ames et al., 1975, Mut. Res. 31:347-364. No further details.

Year : 1980

GLP : No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement

Test substance : Zinc octoate 18%, Lot No. 150

Method : Followed method of Ames et. al.

Method detail : 0.1 mL aliquots of test material at 5 concentrations were used. Positive controls and vehicle controls (ethanol) included. Plates incubated for 48 hours at 37ºC and number of colonies compared to background. No further details provided.

Result : Negative. Test material did not induce a significant increase in the number of revertant colonies over that shown in the solvent control plates for all strains of *S. typhimurium* tested, either with or without activation. Mutagenic

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index of all five strains was less than 2.0. Positive controls produced the expected response.

Remark	:	
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Van Goethem, D., 1980. Evaluation of zinc octoate in the *Salmonella*/Microsome (Ames) assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).
Type	:	Mutagenicity
Guideline/method	:	
System of testing	:	Bacterial DNA damage or repair assay
Species	:	*Escherichia coli*
Strain	:	W3110 (pol A^+) and its DNA polymerase deficient derivative p3478 (pol A^-)
Test concentrations	:	5, 10, 50, 100, and 500 µg/mL, in duplicate. Dissolved in DMSO.
Cytotoxic concentr.	:	
Metabolic activation	:	With and without. Activation with S-9 from Aroclor 1254 induced rat liver per Ames al., 1975, Mut. Res. 31:347-364 .
Year	:	1981
GLP	:	No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement
Test substance	:	Zinc octoate 18%, Lot No. 150
Method	:	Followed method of Rosenkranz et al. (1971).
Method detail	:	Test material (5 concentrations) applied to cells in culture. Vehicle controls (DMSO) included. Positive controls included (N-methyl-N'-nitrosoguanidine at 2 ug/mL without activation and 2-aminofluorene at 200 ug/mL with activation). Bacteria (10^4) of each strain were exposed to the test material for 1 hour at 37ºC. Then 0.1 mL aliquots were removed and plated on agar, with and without activation, incubated for 18 hours at 37ºC and the number of viable cells determined.
Result	:	Negative. No dose-response was observed and there was no decrease in survival index (ratio of pol A^- to pol A^+ survivors), with or without activation. Survival index at all nonprecipitating dose levels was greaten than 0.80. Noted that two highest concentrations (with and without activation) caused a white precipitate to form, hence data from these concentrations not useful.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Van Goethem, D., 1981. Evaluation of zinc octoate, 18%, in the *E. coli* DNA Repair-Suspension Assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:
Guideline/method	:
Species	:
Strain	:
Sex	:
Route of admin.	:
Exposure period	:
Doses	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:

Remark :
Reliability :
Reference :

5.8.2 DEVELOPMENTAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
NOAEL maternal tox. :
NOAEL teratogen. :
Other :
Other :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type :
Guideline/method :
In vitro/in vivo :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

6.0 OTHER INFORMATION

6.1. CARCINOGENICITY

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ROBUST SUMMARIES and SIDS DOSSIER for: 2-Ethylhexanoic Acid

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CAS No. 149-57-5

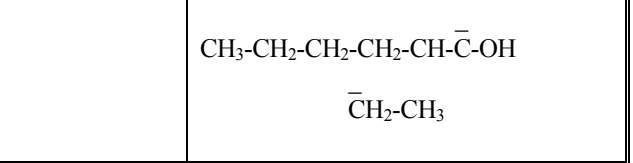
Sponsor Country: U.S.A.

DATE: Revised July 2001

CONTENTS

CONTENTS

SIDS PROFILE

1.1	CAS No.	149-57-5
1.2	CHEMICAL NAME	2-Ethylhexanoic acid
1.5	STRUCTURAL FORMULA	
	OTHER CHEMICAL IDENTITY INFORMATION	
3.0	SOURCES AND LEVELS OF EXPOSURE	No likely exposure of public because this material is used exclusively as an industrial intermediate. Minimal likelihood of dermal exposure to workers during processing.
3.1	PRODUCTION RANGE	5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).
3.3	CATEGORIES AND TYPES OF USE	2-Ethylhexanoic acid is categorized as an intermediate for industrial use (closed system). There is no public or export use.
Issues for discussion		

SIDS SUMMARY

CAS-Number 149-57-5 STUDY	Info. Available Y/N	OECD Study Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
PHYSICAL-CHEMICAL							
2.1 Melting Point	Y	N	N	Y	N	Y	N
2.2 Boiling Point	Y	N	N	Y	N	Y	N
2.3 Vapour Pressure	Y	N	N	Y	N	Y	N
2.4 Partition Coefficient	Y	N	N	N	Y	Y	N
2.5 Water Solubility	Y	N	N	Y	N	N	N
OTHER STUDIES RECEIVED	Y						
ENVIRONMENTAL FATE/BIODEGRADATION							
4.1.1 Aerobic Biodegradability	Y	N	N	Y	N	Y	N
4.1.3 Abiotic Degrability							
4.1.3.1 Hydrolysis	N	-	-	-	-	-	N
4.1.3.2 Photodegradability	N	-	-	-	Y	Y	N
4.3 Env. Fate/Distribution	N	-	-	-	-	-	N
Env. Concentration	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						
ECOTOXICOLOGY							
5.1 Acute Toxicity Fish	Y	N	N	Y	N	Y	N
5.2 Acute Toxicity Daphnia	Y	N	N	Y	-	Y	N
5.3 Acute Toxicity Algae	Y	N	N	Y	-	Y	N
5.6.1 Acute Toxicity Terrest. Organisms	N	-	-	-	-	-	N
5.6.2 Acute Toxicity Terrest. Plants	N	-	-	-	-	-	N
5.6.3 Acute Toxicity Avians	N	-	-	-	-	-	N
5.6.4 Avian Reproduction	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						

CAS No: 149-57-5 STUDY	Info Available Y/N	OECD Summary Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
TOXICOLOGY							
6.1 Acute Oral	Y	Y	N	Y	N	Y	N
Acute Dermal	Y	N	N	Y	N	N	Y
Acute Inhalation	Y	N	N	Y	N	N	N
6.4 Repeated Dose	Y	Y	Y	N	N	Y	N
6.5 Genetic Toxicity							
- Gene Mutation	Y	N	N	Y	N	Y	N
- Chromosome Aberration	Y	-	-	-	-	-	N
6.7 Reproductive Toxicity	Y	N	Y	-	-	Y	N
OTHER STUDIES RECEIVED	Y						

Summary of Responses to the OECD Request for
Available Data on HPV Chemicals

1.0 General Information

Name of Sponsor Country: United States of America

Contact Point:

Mr. Charles Auer
Director - Existing Chemicals Assessment Division
Office of Toxic Substances (TS-788)
U S Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
Telephone (202) 382-3442
Fax (202) 382-7883, -7884, -7885

Name of Lead Organization: US Environmental Protection Agency

2.0 Chemical Identity

* 2.1 **CAS Number:** 149-57-5

* 2.2 **Name** (Name Supplied by the OECD): 2-Ethylhexanoic acid

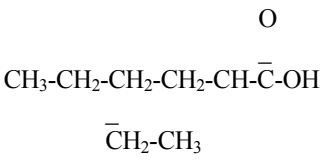
2.3 **Common Synonyms:**

α-Ethylcaproic acid
2-Ethylcaproic acid
α-Ethylhexanoic acid
Butylethylacetic acid
Ethylhexoic acid
2-EHA
2-EH acid
2-Ethylhexoic acid
2-Ethylhexanoic acid
2-Butylbutanoic acid
2-Heptanecarboxylic acid
3-Heptanecarbolic acid
Octanoic acid

2.4 **Empirical Formula:**

$C_8H_{16}O_2$

* 2.5 **Structural Formula:**



2.6 **Purity of Industrial Product**

2.6.1 **Degree of Purity** (Percentage by Weight/Volume): 99% by weight

2.6.2 **Identity of Major Impurities** (Typical Analysis): None detected.

2.6.3 **Essential Additives** (Stabilizing Agents, Inhibitors, Other Additives), if applicable: Not applicable.

3.0 **Physical-Chemical Data**

* 3.1 **Melting or Decomposition Point:** -118.4°C (melting point)

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.2 **Boiling Point** (Including Temperature of Decomposition, If Relevant): 227.6°C

Method: (e.g., OECD, Others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.3 **Vapor Pressure:**

1.33×10^{-3} kPa at 20°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.4 (A.) **Partition Coefficient n-Octanol/Water** (Preferred Study)

log Pow = 3 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Lyman, W.J., Reehl, W.F., and Rosenblatt, D.H. (1982). Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds, Chapter 1. McGraw-Hill, New York.

(B.) **Partition Coefficient n-Octanol/Water (Additional Information)**

log Pow = 2.64 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Pamona College Medicinal Chemistry Project, Claremont, CA

* 3.5 **Water Solubility:**

25 mg/L at 25°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Analytical Method: None provided.

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.6 **Flash Point (Liquids):** 118°C

closed cup [ ] open cup [X]

Method:

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.7 **Flammability**

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Test Results: Autoignition temperature = 371°C

Cool flame autoignition = 199°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.8 **pH in Water**

pH at mg/L (Water)

pKa = 4.8 at 25°C

Method (e.g., OECD, others): Not provided.

GLP: YES [ ]
NO [X]

Comments: Data predates GLP regulations.

Reference: Product literature, Union Carbide Corp. (1974).

3.9 **Other Data**

Density: 0.90 cc at 20°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

4.0 **Source of Exposure**

* 4.1 **Production Levels Expressed as Tonnes Per Annum:** 5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).

4.2 **Processes:** 2-Ethylhexanoic acid is manufactured by the air oxidation of 2-ethylhexaldehyde, using a continuous enclosed computer-controlled process. The crude product is purified by extractive removal of water-soluble impurities and by distillation. The product is transferred through closed, dedicated lines to storage tanks.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

* 4.3 **Information Concerning Uses** (including categories and types of uses expressed in percentage terms): The primary use for 2-ethylhexanoic acid is as an industrial intermediate for chemical conversion to metallic salts, which are used as paint dryers. The substance may also be used as an industrial intermediate in the manufacture of catalysts, plasticizers, inks and dyestuffs, drugs, flame retardants, surfactants and lubricants. 2-Ethylhexanoic acid is not sold as a consumer formulation in the United States.

4.4 **Options for Disposal:** Non-aqueous wastes are incinerated and aqueous wastes are sent to a waste-water treatment facility for biodegradation.

4.5 **Other Remarks:**

Information Concerning Human Exposure: Approximately 400 people may be exposed to 2 ethylhexanoic acid during manufacture and use in the United States. Because 2-ethylhexanoic acid has a low volatility, the potential for atmospheric release or inhalation exposure is minimal. Dermal exposure is minimized by the enclosed, automatic nature of the manufacturing process, and bulk handling and transfer. The potential dermal exposure is further minimized by requiring all workers to wear dermal protection, such as impermeable gloves, when taking four-ounce quality control samples (which is an approximately 2-minute operation, conducted by one worker about eight times daily).

Shipment of 2-ethylhexanoic acid to customers is primarily by tank car or tank truck. A small percentage (approximately 3%) is shipped in drums. Customers typically receive the material through closed lines, and store in tanks prior to use. The substance is subsequently transferred to enclosed reactors for chemical conversion to other substances. Beyond this point, there is no exposure to 2-ethylhexanoic acid, as it ceases to exist as a chemical.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

5.0 Environmental Fate and Pathways

* 5.1 **Degradability (Biotic and Abiotic)**

5.1.1 **Biodegradability**

Test Substance: 2-Ethylhexanoic acid

Test Type: aerobic [X], anaerobic [ ]

Test Medium: Activated, non-acclimated sludge

In the case of poorly soluble chemicals, treatment given (nature, concentration, etc.):

Test Method: According to Price, K.S., Waggy, G.T., and Conway, R.A. (Brine Shrimp Bioassay and Seawater BOD of Petrochemicals, J. Water Poll. Control Fed. 46, 63-77, 1974). Similar to OECD Guideline 301D. Concentrations of 3, 7, and 10 mg/L used. BOD determined after 5, 10, and 20 days.

GLP: YES [ ]
NO [X]

Test Results: BOD_5 = 60 % of Theoretical (2.44 g O_2/g test substance).
BOD_{10} = 76 % of Theoretical (2.44 g O_2/g test substance).
BOD_{20} = 83 % of Theoretical (2.44 g O_2/g test substance).

Comments: Study predates GLP regulations.

Reference: G.T. Waggy. 1994. Union Carbide Chemicals and Plastics Company, Inc., South Charleston, WV.

5.1.2 **Sewage Treatment**

Comments: No Data Available.

5.1.3 **Stability in Air** (e.g., photodegradability)

Test Substance:

Test Method or Estimation Method (e.g., OECD, others): Calculation

GLP: YES [ ]
NO [X]

Test Results: 2-Ethylhexanoic acid is not expected to enter the air as a vapor due to its low vapor pressure.

Reference: Staples, 2000.

5.1.4 **Stability in Water** (e.g., hydrolysis):

Test Substance:

Test Method: Calculation

GLP: YES [ ]
NO [X]

Test Results: See Staples report.

Reference: Staples, 2000.

5.1.5 **Identification of Main Mode of Degradability in Actual Use**

No Data Available.

5.2 **Bioaccumulation**

Test Substance:

Test Method (e.g., OECD, others): Calculated

GLP: YES [ ]
NO [X]

Test Results: see Staples report

Bioaccumulation Factor:

Calculated Results:

Comments:

Reference: Staples, 2000.

* 5.3 **Transport and Distribution between Environmental Compartments Including Estimated Environmental Concentrations and Distribution Pathways**

Because of its low vapor pressure (see Section 3.3), 2-Ethylhexanoic acid is not expected to be transported to the air. Transport to soil is possible where biodegradation is expected since 2-Ethylhexanoic acid is readily biodegradable (see Section 5.1).

Type of Transport and Distribution Processes between Compartments (e.g., air, water, soil):

Distribution to water is not expected because 2-Ethylhexanoic acid has a low water solubility (see Section 3.5).

Estimation of Environmental Concentrations:

Reference: Staples, 2000.

5.4 **Monitoring Data** (Environment):

No Data Available.

6.0 Ecotoxicological Data

* 6.1 **Toxicity to Fish**

6.1.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Pimephales promelas (fathead minnow)

Test Method: Test method 231, Toxicity to Fish, in Standard Methods for the Examination of Water and Wastewater (1971). Ten adult minnows per concentration were exposed for 96 hours.

· Type of test static [X], semi-static [ ], flow-through [ ]
Other (e.g., field observation) [ ]

GLP: YES [ ]
NO [X]

Test Results: LC_{50} = 70 mg/L after 96 hours at a pH of 5.3-5.5

Comments: Study predates GLP regulations. Test solutions were not buffered.

Reference: Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

6.1.2 **Results of Long-Term Tests** e.g., prolonged toxicity, early life stage

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.2 **Toxicity to Daphnids**

6.2.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Daphnia magna (waterflea)

Test Method (e.g., OECD, others): Daphnid Acute Toxicity Test - "Guideline For Testing Chemicals", EG-1, EPA, Office of Toxic Substances, Jan. 1982, 75-009 (1975).

Test Concentration: 31.25, 62.5, 125, 250, & 500 mg/L.

Test Duration: 48 hours.

GLP: YES [ ]
NO [X]

Test Results: 48 hr EC_{50} = 85.38 mg/L (slightly toxic),
CI 95% = 79.77-91.38 mg/L
48 hr EC_0 = 62.5 mg/L, 48 hr EC_{100} = 125 mg/L

Comments: No analytical measurements available. Tested at nominal concentrations ranging from 31.25-500 mg/L. (EC_0 - highest tested concentration without effect after 48 hours. EC_{100} - lowest tested concentration with 100% effect after 48 hours).

Reference: BASF Aktiengessellschaft Report # 1/0949/2/88 - 0949/88 dtd. 04-11-1988. Entitled "Determination of the Acute Toxicity of 2-Ethylhexansaeure to the Waterflea *Daphnia magna straus*."

6.2.2 **Results of Long-Term Tests e.g., Reproduction**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.3 **Toxicity to Algae**

Test Substance: 2-Ethylhexanoic acid

Test Species: Scenedismus subspicatus

Test Method (e.g., OECD, others): Inhibition of Algal Replication Following DIN 38412 L9.

Test Concentration: 0, 25, 50, 100, 250, or 500 mg/L.

Test Duration: 96 hours.

GLP: YES [ ]
NO [X]

Test Results: 72 hr EbC_{10} = 32.543 mg/L
72 hr EbC_{50} = 60.511 mg/L

96 hr EbC_{10} = 24.496 mg/L
96 hr EbC_{50} = 40.616 mg/L

72 hr EuC_{10} = 31.940 mg/L
72 hr EuC_{50} = 49.279 mg/L

96 hr EuC_{10} = 27.938 mg/L
96 hr EuC_{50} = 44.390 mg/L

Comments: Nominal concentrations tested. No analytical available on test concentrations.

Reference: BASF AG. Report # BASF 2/0949/88, dated 10/24/1989.

6.4 **Toxicity to Other Aquatic Organisms**

Test Substance:

Test Species:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

6.5 **Toxicity to Bacteria**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.6 **Toxicity to Terrestrial Organisms**

6.6.1 **Toxicity to Soil Dwelling Organisms**

Test Results: No Data Available.

6.6.2 **Toxicity to Plants**

Test Results: No Data Available.

6.6.3 **Toxicity to Birds**

Test Results: No Data Available.

6.7 **Biological Effects Monitoring (Including Biomagnification)**

Test Results: No Data Available.

6.8 **Biotransformation and Kinetics in Environmental Species**

No Data Available.

7.0 **Toxicological Data** (oral, dermal and inhalation, as appropriate)

* 7.1 **Acute Toxicity**

7.1.1 (A.) **Acute Oral Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Male Wistar Rats

Test Method: Groups of 6 rats were treated by gavage with 2-ethylhexanoic acid in water. Animals were observed for mortality over the course of fourteen days.

GLP: YES [ ]
NO [X]

Test Results: Discriminating dose (for fixed dose only): LD_{50} = 3000 g/kg

Comments: Study predates GLP regulations. Body weights not measured; clinical signs of toxicity not described. No information provided on dosing solution.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Oral Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rats/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Two animals (sex not specified) per group were treated with either 100, 200, 400, 800, 1600, or 3200 mg/kg by gavage and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: Transient signs of weakness and ataxia immediately after dosing were described. There was no effect on body weight.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments: Study predates GLP regulations. Test sample not analyzed. Onset and duration of clinical signs of toxicity not indicated. Body weight data not provided. Preparation of dosing solution not indicated. No indication of fasting.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(C.) **Acute Oral Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.6%) in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method: Eastman Kodak Company, Health and Environment Laboratories Protocol. Non-fasted animals (4 per group) were treated with either 0, 100, 800, 1600, or 3200 mg/kg in a single dose by gavage and observed for 14 days.

GLP: YES [X]
NO [ ]

Test Results: Animals treated with 800, 1600, and 3200 mg/kg appeared slightly to severely weak immediately after dosing. Animals given 3200 mg/kg were prostrate 4 hours after treatment. Animals in the other groups were normal immediately after dosing. By 24 hours post-treatment, animals treated with 3200 mg/kg died, but all other animals appeared normal. All surviving animals gained weight. No gross pathology was observed in any surviving animal, and animals that died on test had no distinctive gross pathology.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments:

Reference: Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Health and Environment Laboratories, Eastman Kodak Company.

7.1.2 **Acute Inhalation Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rat/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Three rats (sex not specified) exposed to nominal concentration of 2.36 mg/L (400 ppm) for 6 hours and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: No mortality or clinical signs of toxicity occurred. Animals gained weight.

LC50: NA

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.1.3 **Acute Dermal Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: Guinea pig/strain not specified

Test Method: Six animals (sex not specified) were treated with the test material in an occluded patch for four days and observed for a total of 14 days.

GLP: YES [ ]
NO [X]

Test Results: LD50: 6.5 ml/kg

Comments: Study predates GLP regulations. No clinical observations cited. Body weights not measured.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Dermal Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for mortality. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Both animals receiving neat (undiluted) 2-ethylhexanoic acid died. No mortality occurred with the 20% preparation, but the animal receiving 20 ml/kg of the 20% preparation lost weight.

LD50: < 5.0 ml/kg

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.2 Corrosiveness/Irritation

7.2.1 Skin Irritation

(A.) **Test Substance**: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for irritation. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Slight edema, erythema, and necrosis was observed with neat material. No edema or very slight edema, with slight to moderate redness, was observed after treatment with the 20% solution.

Comments: Study predates GLP regulations.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(B.) **Skin Irritation** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: New Zealand White Rabbit

Test Method: US Department of Transportation Corrosivity Test

GLP: YES [X]
NO [ ]

Test Results: The test material produced slight necrosis in 5 of 6 animals after 4 hours with subsequent eschar formation (slight to moderate).

Comments:

Reference: Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Health and Environment Laboratories, Eastman Kodak Company.

7.2.2 **Eye Irritation**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rabbit/strain not designated

Test Method (e.g., OECD, others): Volumes of 0.001, 0.005, 0.02, 0.1, or 0.5 mL were instilled into the eye of albino rabbits and the eyes evaluated after 24 hours using fluorescein stain.

GLP: YES [ ]
NO [X]

Test Results: Severe corneal irritation was observed

Comments: Study predates GLP regulations. No indication of the number of animals used. No indication of the extent of irritation or corneal opacity. No observation beyond 24 hours to indicate recovery.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

7.3 **Skin Sensitisation**

Test Substance:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.4 **Repeated Dose Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides. The liver was analyzed biochemically for peroxisome activity and evaluated microscopically for the presence of peroxisomes.

GLP: YES [ ]
NO [X]

Test Results: Animals fed the diet containing 2-ethylhexanoic acid gained 15% less weight than did control animals. Relative (to body weight) liver weight was 55% higher in treated animals compared with control animals. Liver catalase and carnitine acetyltransferase activities were significantly increased in treated animals. The ratio of mitochondria to peroxisomes was approximately 1:1 compared with the control animals which had a ratio of 5:1, indicating a substantial increase in peroxisome proliferation. Cholesterol and triglyceride levels were significantly decreased.

Comments: No indication of absolute liver weight given. No data of triglyceride and cholesterol levels provided. Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1978). Hepatic Peroxisome (Microbody) Proliferation in Rats Fed Plasticizers and Related Compounds. Toxicol. Appl. Pharmacol. 45, 497-504.

(B.) **Repeated Dose Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides.

GLP: YES [ ]
NO [X]

Test Results: Cholesterol levels in treated animals were 17% below the level in control animals, and triglycerides were 68% less than in controls.

Comments: Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1982). Serum Triglyceride and Cholesterol Contents in Male Rats Receiving Diets Containing Plasticizers and Analogues of the Ester 2-Ethylhexanol. Toxicol. Lett. 10, 379-383.

(C.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: B6C3F1 Mice

Test method: Male and female mice (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: One animal from the mid-dose group was found dead and one control animal was euthanatized in extremis. Gait disturbance and weakness were observed in one high-dose female during the first two days of treatment. All other animals appeared normal except for the control animal that was euthanatized. Body weights and feed consumption were unaffected by treatment. High-dose male mice had increased absolute and relative (to body weight) liver weight which was associated with hypertrophy of the hepatocytes. Liver weight and microscopic morphology of all other groups were comparable to controls. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 800 mg/kg for males and 1600 mg/kg for females.

Comments:

Reference: Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Health and Environment Laboratories, Eastman Kodak Company.

(D.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal

was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Five animals (three male and two female) in the high-dose group were found dead, and three additional animals from this group were euthanatized in extremis. No mortality occurred in other groups. Weakness and lethargy, hypothermia, sialorrhea, tremors, and poor body condition were observed high-dose animals. Mid-dose animals showed weakness, lethargy, and sialorrhea, generally less severe than in the high-dose animals. All other animals appeared normal. Body weights in surviving high-dose animals were 10-20% less than in the control group. Mid-dose male rats also had significantly lower body weight compared with the control group, but mean body weight in mid-dose females and low-dose groups was comparable to the control group. Feed consumption in surviving high-dose animals was decreased, while in all other groups was comparable to controls. High- and mid-dose rats had dose-related increased absolute and relative (to body weight) liver weight. High-dose animals which survived to termination had hepatocyte hypertrophy. Animals that died on test had minimal hepatocyte degeneration. Microscopic morphology of the liver of all other groups were normal. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 200 mg/kg for males and < 200 mg/kg for females.

Comments:

Reference: Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Health and Environment Laboratories, Eastman Kodak Company.

(E.) **Repeated dose toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: Male and female mice (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 1608-1965, 3084-3986, and 5794-9229 mg/kg/day for the low-, mid, and high-dose groups, respectively. One male from the mid-dose group was found dead during

the study. The cause of death was not apparent. All other animals appeared normal. Animals fed 3.0% 2-ethylhexanoic acid lost weight during the first few days, and did not gain weight during the remainder of the study. Males fed the 1.5% diet had lower body weights on Day 14 compared to the control group. Body weights in the other groups were comparable to the control group. Feed consumption was initially reduced in treated groups, but was comparable to the control group thereafter. Absolute and relative (to body weight) liver weight of animals in the high- and mid-dose groups (male and female) were significantly higher than in the control groups. Hepatocyte hypertrophy, primarily in the portal region, was observed in all groups except a few low-dose animals. The severity decreased with dose from moderate in the high-dose groups, to minor in the mid-dose groups, to minimal in the low-dose groups. Coagulative necrosis of the hepatocytes was also observed in treated male groups and in the high-dose female group. The severity was described as minimal and the lesion multifocal. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Health and Environment Laboratories, Eastman Kodak Company.

(F.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, the doses received were 706-756, 1351-1411, and 2276-2658 mg/kg/day for the low-, mid, and high-dose groups, respectively. High-dose animals had slightly reduced amounts of feces on Days 2 and 3, and periodically they appeared unkempt, but no other signs of toxicity were observed. High-dose animals lost weight initially, and had low weight gains during the remainder of the study. Mid-dose male rats also had a reduced weight gain during the study, and had significantly lower body weights only at termination compared with the control group. All other groups gained comparable amounts of weight. Feed consumption was reduced in the high- and mid-dose groups. Absolute and relative (to body weight) liver weight were

significantly increased in a dose-related manner. Hepatocyte hypertrophy and coagulative necrosis were observed in high- and mid-dose animals. The severity and/or incidence of these lesions were lower in the mid-dose group compared with the high-dose group. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Health and Environment Laboratories, Eastman Kodak Company.

(G.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 180-205, 885-1038, and 2728-3139 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose group compared with the control group. Body weights in the high-dose groups were significantly lower than in the control group beginning after the first week, and body weights in mid-dose females were significantly lower than in controls only after 13 weeks. Male mid- and all low-dose groups were unaffected by treatment. No changes in hematology occurred. Cholesterol levels were significantly higher in mid-dose and high-dose mice, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. Bilirubin was significantly lower in the high-dose groups, and in the mid-dose female group, compared with the control group. Incidental changes in urea nitrogen and alanine transaminase were not considered to be treatment-related. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose groups compared with the control groups. Relative (to brain weight) liver weight of male and female mice fed 0.5%, and absolute and relative (to body weight) liver weight of male mice fed 0.5% were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia

were observed in the liver of mid- and high-dose groups after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. High-dose mice also had cytoplasmic basophilia of the proximal convoluted tubules, and male high-dose mice had acanthosis and hyperkeratosis of the non-glandular forestomach. All toxicity was reversible within 28 days. The no-observable-adverse-effect level (NOAEL) was 0.1% 2-ethylhexanoic acid in the diet (approximately 200 mg/kg/day). A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Health and Environment Laboratories, Eastman Kodak Company.

(H.) **Repeated Dose Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer 344 Rats

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney,

adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day).

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Health and Environment Laboratories, Eastman Kodak Company.

* 7.5 **Genetic Toxicity**

7.5.1 **Bacterial test**

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: S. typhimurium TA98 and TA100, with and without S-9

Test Method: Incubation with test substance for 2 days at 37°C in standard Ames test.

GLP: YES [ ]
NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation:	2.9 mg/plate
without metabolic activation:	2.9 mg/plate

Concentration of the test compound resulting in precipitation: Not determined

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: No control values provided.

Reference: Warren, J.R., Lalwani, N.D., and Reddy, J.K. (1982).

Phthalate Esters as Peroxisome Proliferator Carcinogens. Environ. Health Perspec. 45, 35-40.

(B.) **Bacterial Test** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid in DMSO

Test Species/Strain: Salmonella typhimurium/TA-97, TA-98, TA-100, and TA-1535.

Test Method: Modified from Haworth et al., 1983. Environ. Mutagen 5 (Suppl 1):3-142. Concentrations of S-9 from rats or hamsters treated with Aroclor 1254 varied between 10 and 30%.

GLP: YES [ ]
NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: 3.3 mg/plate
without metabolic activation: 3.3 mg/plate

Concentration of the test compound resulting in precipitation:

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: Conducted as part of Government contract. Not under GLP regulations.

Reference: Zeiger, E., et al., (1988). Salmonella Mutagenicity Test: IV. Results From the Testing of 300 Chemicals, Environ. Mol. Mutagen. 11, 1-158.

7.5.2 **Non-Bacterial *In Vitro* Test**

Test Substance:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

7.5.3 **Non-Bacterial Test *In Vivo***

Test Substance: 2-Ethylhexanol in corn oil (see comments)

Test Species/Strain: Mouse/B6C3F1

Test Method (e.g., OECD, others): Micronucleus test - Six male and six female mice were injected intraperitoneally with either a once or twice within 24 hours with 456 mg/kg. Control groups (same numbers/sex) received corn oil only. A positive control group received triethylene melamine. Micronuclei were determined in the polychromatic erythrocytes.

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GLP: YES [X]
NO [ ]

Test Results: There were no increased incidences of micronuclei in polychromatic erythrocytes in the female groups receiving 2-EH. The male group that received a single intraperitoneal injection of 456 mg/kg 2-EH did not have an increased incidence of micronuclei in polychromatic erythrocytes. An increased incidence of micronuclei in the male group that received two intraperitoneal injections of 456 mg/kg 2-EH was attributed to an unusually low incidence of micronuclei in the control group. The values for all the treated groups (up to 0.28%) were within the normal range for the testing laboratory.

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Comments: The data from 2-ethylhexanol is directly applicable to the assessment of this endpoint for 2-ethylhexanoic acid due to the extensive metabolism of the former to the latter in vivo. (Other studies with 2-ethylhexanol are available and listed in the SIDS Dossier for that chemical; however, this study seemed the most relevant).

Reference: Litton Bionetics Inc., (1982) Mutagenicity Evaluation of 2-ethylhexanol (2-EH) in the mouse micronucleus test. See also CMA Communication from the Chemical Manufacturers Association to the Employment Accident Insurance Fund of the Chemical Industry. (1982). (See also EPA OTS508477)

7.6 **Carcinogenicity**

Test Substance:

Test Species/Strain:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.7 **Reproductive and Developmental Toxicity**

7.7.1 **Reproductive Toxicity**

Test Substance: Sodium 2-Ethylhexanoate (99.5%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): According to OECD Guideline 415, One-Generation Reproduction Toxicity Study. Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

GLP: YES [ ]
NO [X]

Test Results: The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not

provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

Comments: Water consumption was measured, but the interval was not stated. Water consumption values were not provided to ascertain the extent of unpalatability. The concentration of the test substance in the drinking water was not provided, and there was no analysis of dosing solutions. The incidence of an effect within an animal (such as for sperm morphology) or litter (such as for kinky tail) was not provided. Such information would be helpful to evaluate if the effects are nested in single individuals or litters.

Also, no criteria were provided to indicate how many abnormal sperm were necessary to be considered a positive response. This involved only a few animals, and whether the effect involved specific males or females was not identified. Since all animals were naive and not proven breeders, reduced mating success may not be treatment related. It is also not known how much the unpalatability of treated drinking water stressed the animals. No confirmation of estrous cycle was performed. No data on the effect of the test substance on gestation period were presented. Thus, the apparent effect on physical development of pups from the high-dose group dams may be the result of early delivery which could present the appearance of a slight delay in development. The variability of the data for sperm numbers and motility was as high as 50% and was not considered to be reproducible between animals in a group to be a reliable indicator of male function.

Histopathology of reproductive organs in the Repeated Dose Studies in Sprague-Dawley rats did not indicate any morphologic changes even after 13 weeks of dietary treatment with doses of approximately 1000 mg/kg/day. Developmental toxicity studies in Fischer-344 rats or NZW rabbits have not indicated any early fetal mortality or effects on viable or non-viable litter size. Wistar rats have demonstrated a susceptibility to the developmental effects of this test substance.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., Kosma, V.-M., and Komulainen, H. (1993). Effects of 2-Ethylhexanoic acid on Reproduction and Postnatal Development in Wistar Rats. Fundam. Appl. Toxicol. in press.

7.7.2 (A.) **Teratogenicity/Developmental Toxicity**

Test Substance: 2-Ethylhexanoic acid (neat)

Test Species/Strain: Wistar Rats

Test Method (e.g., OECD, others): Seven to ten pregnant females per group were treated by gavage with a single dose of either 0, 1.0, or 2.0 ml/kg 2-ethylhexanoic acid (approximately 900 or 1800 mg/kg) on Day 12 of gestation and dams euthanatized on Day 20. Fetuses were preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [ ]
NO [X]

Test Results: The high dose produced embryo- and fetal-toxicity based on the 30% decrease in fetal weight, and 30% increased in percentage dead and resorbed fetuses (from 9.6 in controls to 12.9 in the high-dose). The percentage of malformed fetuses increased from 0 in control animals to 67.8% in the high dose dams. No apparent toxic or teratogenic effect was observed at the low dose. Defects observed included hydronephrosis, levocardia, septal defects, short and kinky tail, ectrodactyly, misplaced digits, and bowed radius.

The percentages of surviving fetuses with anomalies are: 20.9% hydronephrosis; 10.1% cardiovascular; 15.5% tail (skeletal); 51.2% limb (skeletal); and 10.9% other (not specified).

NOEL for maternal animals = Not determined

NOEL for offspring = 0.9 g/kg

Comments: Maternal effects were not described. There was no indication of effects on sex of fetuses. The number of animals per group is low (only 7), and fetal data are presented as percentages of affected fetuses per litter. Thus, one or two litters could have adversely affected the data. No data of anomalies in control animals were presented. There was no analysis of dosing solutions.

Reference: Ritter, E.J., Scott, Jr., E.J., Randall, J.L., and Ritter, J.M. (1987). Teratogenicity of Di(2-ethylhexyl) Phthalate, 2-Ethyhexanol, 2-Ethylhexanoic Acid, and Valproic Acid, and Potentiation by Caffeine. Teratol. 35: 41-46.

(B.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: Han:NMRI Mice

Test Method (e.g., OECD, others): Nine to 20 pregnant female mice were injected ip with a total dose of 500 or 2000 mg/kg/day (4 x 500 mg/kg per day) of sodium 2-ethylhexanoate (racemic mixture and R- and S-enantiomers) on Day 8 of gestation. Dams were sacrificed on Day 18 and examined for the number of implantations, live and dead fetuses, and early resorptions. Live fetuses were weighed and examined for exencephaly.

GLP: YES [ ]
NO [X]

Test Results: A dose of 2000 mg/kg/day of the (R) enantiomer or racemic mixture produced ~10% embryolethality and 16% lower fetal weight. Of the total fetuses examined in these groups, 32 and 59% had exencephaly (racemic mixture and (R) enantiomer, respectively). There is no indication of the number of litters affected. The same dose of the (S) enantiomer and 500 mg/kg/day of the racemic mixture were not fetotoxic or teratogenic since embryolethality and fetal weight were at control levels.

NOEL for maternal animals = Not determined

NOEL for offspring = 500 mg/kg/day for the racemic mixture, 2000 mg/kg/day for the (S) enantiomer. Not determined for the (R) enantiomer.

Comments: Author states that Han strain of mouse used demonstrates susceptibility to exencephaly. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed four times per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided. There was no analysis of the dosing solutions.

Reference: Hauck, R.-S., Wegner, C., Blumtritt, P., Fuhrhop, J.-H., and Nau, H. (1990). Asymmetric Synthesis and Teratogenic Activity of (R)- and (S)-2-Ethylhexanoic Acid, A Metabolite of the Plasticizer Di-(2-ethylhexyl)phthalate. Life Sci. 46, 513-518.

(C.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): Similar to Guideline 414. Mated female rats were treated from Gestation Days 6-19 with either 0, 100, 300, or 600 mg/kg/day of the test substance in drinking water. Clinical signs of toxicity were observed daily. Body weight was measured weekly. Feed consumption was measured during Gestation Days 13-16. Water consumption was measured during the treatment period, but the frequency was not stated. Dosing solutions were adjusted periodically to maintain the appropriate dose based on changes in body weight. All animals were sacrificed on Day 20 and examined for live and dead fetuses, resorptions, corpora lutea, implantation sites, and pup weights. Half the fetuses were examined for visceral anomalies, while the other half were stained for skeletal examination.

GLP: YES [ ]
NO [X]

Test Results: The pregnancy rate (successful matings) was slightly lower in the mid- and high-dose groups, but the difference was not statistically significant. There were no clinical signs of toxicity. Body weights of high-dose females were reduced 10% on Day 13, and were significantly lower (11%) on Day 20 compared with the control group. Corrected maternal body weights at termination and weight gains of high-dose females were significantly lower than for the control group. The weight of the gravid uterus was not significantly different, however.

Water consumption was also significantly reduced (up to 20% less than controls), but no data were presented. No differences in feed consumption were noted. No gross pathologic changes were noted in dams.

Mean fetal weight per litter was significantly reduced in the mid- and high-dose groups. Mean placental weights were also significantly reduced. There were no effects on the number of live fetuses or resorptions (early or late). No visceral abnormalities were noted. Clubfoot was the only skeletal malformation noted in mid- and high-dose groups, both having significantly higher percentages of affected fetuses per litter (5-6% versus 0%) than in the control group. Some changes in skeletal variations were noted. The percentages of fetuses per litter with wavy ribs were significantly higher in all treated groups compared with the control group, and the percentages of fetuses per litter with reduced cranial ossification were also significantly higher in the low- and high-dose groups compared with the control group. The percentage of fetuses with twisted hind legs was significantly higher in the mid-dose group (7%) compared with the control group (1%). The

number of litters affected were not indicated.

NOEL for maternal animals = 300 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Comments: There is no indication that changes in water consumption were taken into account when adjusting the concentration of the dosing solution. Also, the frequency of water consumption measurement and adjustments in .the concentration of the dosing solution were not indicated. The number of litters affected were not indicated. As a result, litter effects could not be evaluated.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., and Komulainen, H. (1992). The Developmental Toxicity of 2-Ethylhexanoic Acid in Wistar Rats. Fundam. Appl. Toxicol. 19:505-511.

(D.) **Teratogenicity/Developmental Toxicity** (Additional study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: SWV and C57BL/6NCrlBR Mice

Test Method (e.g., OECD, others): Three to 22 pregnant female mice were injected with multiple doses per day of 403 to 1037 mg/kg of sodium 2-ethylhexanoate. The results of four separate experiments are reported: one to evaluate maternal toxicity following a single subcutaneous injection on Gestation Day 8.0 with 807-1037 mg/kg/day of a racemic mixture of test substance; one to compare the response of SWV and C57 mice injected intraperitoneally on Days 7.5, to 9.0 with 1152 mg/kg/day (2 x 576 mg/kg per day) of a racemic mixture; one comparing the fetotoxicity in animals injected intraperitoneally on Gestation Days 7.0-10.0 with total dose of 1728 mg/kg given as three injections of 576 mg/kg of a racemic mixture over a 36 hour period; and one comparing the fetotoxicity of a total dose of 1209-2592 mg/kg (given as 3 injections of 403-864 mg/kg over 36 hour period) the (S) and (R) enantiomers injected ip on Days 8.0-9.0.

Deleted: e

GLP: YES [ ]
NO [X]

Test Results: Three dams injected sc on Gestation Day 8 with 807 mg/kg of a racemic mixture of sodium 2-ethylhexanoate survived to Day 18, but mortality occurred at 864 and 1037 mg/kg/day (1/7 and 5/6, respectively). Three additional dams injected on Day 8.5 with 864 mg/kg also survived to Day 18. The authors also provide data on the number of resorptions versus implantation sites in these animals. These data indicate that the percentage of resorptions increased at higher dose levels, and was also high in the animal that survived the 864 mg/kg dose on Day 8.5. However, no control

data were provided for comparison.

A comparison of the susceptibility of the SWV and C57 strains indicated that after 4 consecutive injections with 1152 mg/kg/day (racemic mixture) on Days 7.5, 8.0, 8.5, and 9.0, the SWV strain had 49% exencephaly (51/104 live fetuses) compared to 7.3% (6/82 live fetuses) in the C57 strain. The SWV strain also had a significant increase in the number of dead or resorbed fetuses compared with the control group. No such increase occurred in the C57 strain.

Using the SWV strain, the most susceptible period of gestation was determined by three consecutive ip injections of the racemic mixture (total dose of 1728 mg/kg; 3 doses of 576 mg/kg over 36 hour period) on Days 7.0, 7.5, and 8.0 up to 9.0, 9.5, and 10.0, increasing in half-day intervals. The results indicate that the most susceptible time period for producing exencephaly was Days 8.0, 8.5, and 9.0. Treatment with 576 mg/kg during this time produced 44% exencephaly (46/105 live fetuses). Subsequently, pregnant females were treated with a total dose of 1209-2592 mg/kg (3 x 403-864 mg/kg over 36 hrs) of either the (S) or (R) enantiomer during Days 8.0, 8.5, and 9.0. No exencephaly was observed at 1701 mg/kg (3 x 567 mg/kg/36hrs) of the (S) enantiomer, and only 18% (10/56 live fetuses) at 2592 mg/kg (3 x 864 mg/kg/36hrs). Using the (R) enantiomer, a dose of 1728 mg/kg (3 x 576 mg/kg/36hrs) produced 50% exencephaly (53/106 fetuses), while a dose of 1554 mg/kg (3 x 518 mg/kg/36hrs) produced 33% (28/84) exencephaly. A dose of 1209 mg/kg (3 x 403 mg/kg/36hrs) was without effect.

NOEL for maternal animals = 864 mg/kg/day

NOEL for offspring = < 1152 mg/kg/day for C57 strain using the racemic mixture, 1209 mg/kg (3 x 403 mg/kg/36hrs) for (R) enantiomer in SWV strain and 1728 mg/kg (3 x 576 mg/kg/36hrs) for (S) enantiomer in SWV strain.

Comments: Non-standard strain of mouse (SWV) used with no indication of susceptibility to known teratogens. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed twice per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided other than mortality. There was no analysis of the dosing solutions.

Reference: Collins, M.D., Scott, W.J., Miller, S.J., Evans, D.A., and Nau, H. (1992). Murine Teratology and Pharmacokinetics of the Enantiomers of Sodium 2-Ethylhexanoate. Toxicol. Appl. Pharmacol. 112:257-265.

(E.) **Teratogenicity/Developmental Toxicity** (Preferred study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Fischer 344 Rats

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Twenty-five pregnant females per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [X]
NO [ ]

Test Results: No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight was noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters were significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsels, or unossified sternebrae occurred primarily in the high-dose

group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(F.) **Teratogenicity/Developmental Toxicity** (Preferred Study - part of previous study. Note broke out robust information for Fischer Rats and New Zealand Rabbits)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: New Zealand White Rabbits

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

GLP: YES [X]
NO [ ]

Test Results: One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption by 32%) compared with the control group. No differences in liver weight

were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(G.) **Teratogenicity/Developmental toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method (e.g., OECD, others): Mechanistic studies were conducted to investigate the role of maternal hepatic metallothionein (MT) induced in response to administration of 2-ethylhexanoic acid (2EHA) on plasma zinc levels and zinc delivery to the conceptus. In the first experiment, pregnant rats on dietary regimens containing adequate Zn were dosed with 0, 3.1, 6.3, 9.4, or 12.5 mmol/kg (0, 446, 907, 1353, or 1800 mg/kg) 2-ethylhexanoic acid on gestation day (GD) 11.25. Eight hours after dosing, the dams were intubated with radiolabeled Zn. After 10 hours (GD 12.0), the dams were killed and maternal liver MT, radiolabeled zinc distribution and reproductive parameters were assessed. In the second experiment, pregnant rats assigned to dietary regimens containing low, adequate, or supplemental Zn, were intubated with 3.5 mmol 2EHA/kg/day (approximately 500 mg/kg/day in a corn oil vehicle) from gestation days (GD) 8-15. Dams were killed on GD 16, approximately 18 hours after the last dose. Maternal livers were analyzed for Zn and MT concentrations. Maternal plasma was analyzed for zinc concentrations. Fetal development was also assessed. In the third experiment, pregnant rats were divided into three groups and fed diets as described for the second experiment. The animals were also intubated with 2-ethylhexanoic acid in the same manner as the second experiment. Dams were killed on GD 19 and the fetal

parameters were assessed.

The fourth experiment used in vitro embryo culture techniques to explore whether sera from animals dosed with 2-ethylhexanoic acid (9.38 mmol/kg; 1350 mg/kg)was teratogenic, if sera from animals fed diets either marginal or adequate for zinc affected in vitro development of embryos, and if the direct addition of zinc to the sera would prevent the abnormalities from occurring.

GLP: YES [ ]
NO [X]

Test Results: The results of the first of the series of experiments demonstrated that maternal liver MT and Zn concentrations increased at all levels of 2-ethylhexanoic acid administered. The results were statistically significant at the three highest doses administered. Even at the lowest dose, the maternal liver MT and Zn levels were approximately twice those of controls but the results were not statistically significant. Embryonic Zn levels were decreased at the three highest dose levels; the results were statistically significant at the two highest doses administered. The results of the second experiment indicated that 2-ethylhexanoic acid induced hepatic MT and hence sequestered Zn in the maternal liver. Under conditions of zinc stress (marginal Zn in the diet), hepatic induction of MT resulted in lowered plasma Zn levels. The teratogenicity of 2-ethylhexanoic acid (encephalocele, tail defects) was enhanced by dietary Zn deficiency and ameliorated by Zn supplementation. The developmental abnormalities and effect of zinc status from the second experiment were confirmed in GD 19 fetuses from the third experiment. The in vitro development of embryos under conditions resulting in decreased serum Zn (Zn marginal diets alone, Zn marginal diets with 2-ethylhexanoic acid administration, Zn adequate diets with 2-ethylhexanoic acid administration), revealed retarded development of the heart, hind- and forebrain, otic, optic and olfactory systems and fore- and hindlimbs. Direct addition of Zn to the Zn deficient sera (from the conditions described previously) resulted in embryonic development similar to controls. Collectively, these results support the hypothesis that 2-ethylhexanoic acid is causing developmental toxicity indirectly and that developmental toxicity will only occur at dose levels that cause maternal liver toxicity and disrupt Zn metabolism and distribution.

NOEL for maternal animals = Not Determined

LOEL for maternal animals = 446 mg/kg

NOEL for offspring = 446 mg/kg

Comments: The mechanistic studies of 2-ethylhexanoic acid developmental toxicity are of importance since it has been determined that maternal hepatic toxicity is responsible for the adverse fetal outcome. Dose

levels of 2-ethylhexanoic acid that do not affect maternal serum Zn concentrations should not cause developmental toxicity. It appears that several thresholds must be overcome before developmental toxicity resulting from 2-ethylhexanoic acid exposure occurs.

The first threshold is the dose of 2-ethylhexanoic acid must be large enough to cause an acute phase response in the maternal liver and induce hepatic MT production. The second threshold is when the dose of 2-ethylhexanoic acid causes enough hepatic toxicity and MT induction to decrease maternal serum Zn concentrations. The third threshold is when the decrease in maternal serum Zn concentrations becomes severe enough to prevent adequate amounts of Zn from reaching the developing conceptus. The presence of these thresholds are critical in the risk assessment process for 2-ethylhexanoic acid since exposure to this material typically is low.

Reference: Taubeneck, M.W., J.Y. Uriu-Hare, J.F. Commisso, A.T. Borschers, L.M. Bui, W.Faber and C.L. Keen. (1996) Maternal Exposure to 2-Ethylhexanoic Acid (EHXA), 2-Ethylhexanol (EHXO), and Valproic Acid (VPA) Results in Alterations in Maternal and Embryonic Zinc Status. Teratology 53(2):p88, Abstract 21.

7.8 **Specific Toxicities (Neurotoxicity, Immunotoxicity etc.)**

No data available.

7.9 **Toxicodynamics, Toxico-Kinetics**

Test Substance: [2-^{14}C-hexyl] 2-Ethylhexanoic acid (99.6%; 25 mCi/mmole) in corn oil

Test Species/Strain: Female Fischer 344 Rats

Test Method: Similar to USEPA TSCA Health Effects Testing Guideline (CFR 40 798.7100). Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days of oral unlabeled 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

GLP: YES [X]
NO [ ]

Test Results: Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and 1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid 7% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid 14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 7% unmetabolized 2-Ethylhexanoic acid
Oral	100 mg/kg (Repeated)	12% glucuronide-2-Ethylhexanoic acid 12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 5% unmetabolized 2-Ethylhexanoic acid

Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid 3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid 9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid

Comments:

Reference: English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Health and Environment Laboratories, Eastman Kodak Company.

8.0 **Experience with Human Exposure** (Give Full Description of Study Design, Effects of Accidental or Occupational Exposure, Epidemiology)

8.1 **Biological Monitoring** (including clinical studies, case reports, etc.)

A case report of workers employed in Finnish sawmills using a wood preservative containing the sodium salt of 2-EHA has been reported (Kröger, et al., 1990). Use of the wood preservative (26% sodium salt of 2-EHA) was by through-dipping or spray irrigation of the wood followed by drying in a 60°C oven. The spray irrigation methodology recycled the wood preservative solution and used vacuum pressurization in an attempt to reduce exposure. The spray irrigation methodology was more efficient than the through-dipping method for treating wood. Job descriptions included machine stacking, straightening, loading (including working in the oven), working under a crane, working in a crane, and cleaning. Exposure was by the dermal or inhalation route. Sampling from the breathing zones were used to determine air levels for inhalation exposure and patch samples were used to determine dermal exposure. An additional area sample from near the dipping pool was included. Urine samples were collected after the working day until the following morning. Protective clothing ranged from coveralls to street clothes. One worker (of 19) used disposable masks and a few used protective gloves (made of leather or natural rubber). Breathing zone air concentrations ranged from 0.01 (lower detection limit) to 0.70 mg/m^3 (0.0017 to 0.12 ppm). Breathing zone air concentrations from the spray irrigation method were about twice as high as with the through-dipping operation. Patch testing from the outer and inner surface of clothes resulted in a mean of approximately 24 or 7.6 mg 2-EHA deposited per hour, respectively. For comparison, 2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA). Urinary concentrations of 2-EHA ranged from 0.01 to 5.4 mmol 2-EHA/mole creatinine. The highest concentrations of 2-EHA in the urine were found in the samples collected immediately after the work shift, indicating rapid elimination of the material. No urine samples were collected during the work shift. Urinary concentrations correlated

linearly with measured air concentrations but not with the amount found on the patch samples from the clothing of the workers. The authors therefore considered inhalation to be the primary route of exposure. The highest urinary concentrations were found in the crane operators that worked above the through-dipping pools and did not have dermal exposure. Assuming a worst-case exposure scenario (8 hour exposure to 0.7 mg/m^3; 0.0007 mg/L), a breathing rate of 20 Liters/8 hour workday, and 100% absorption of inhaled 2-EHA vapor; an internal dose of 0.014 mg 2-EHA would be achieved. Assuming a 60-70 kilogram person, the dose rate would be 2-2.33 x 10^{-4} mg/kilogram body weight/8 hour workday. The lowest NOEL from the animal studies is 100 mg/kg. Therefore, the dose resulting from the worst-case exposure scenario is approximately 430,000-fold lower than the lowest NOEL from the laboratory studies.

Reference: Kröger, S., Liesivuori, J., and A. Manninen (1990) Evaluation of Worker's Exposure to 2-Ethylhexanoic Acid (2-EHA) in Finnish Sawmills. Int. Arch. Occup. Environ. Health, 62:213-216.

9.0 Recommended Precautions, Classification (Use and/or Transportation) and Safety Data Sheets

2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA).

10.0 Availability and Reference(s) for Existing Review(s)

APPENDIX A

The reports listed in this Appendix are arranged according to the section to which they refer. For reports that are used in multiple sections as indicated by an asterisk (*), only one copy of the report is included and can be found in the first section heading for which it is referenced.

(*)G.T. Waggy, Union Carbide Chemicals and Plastics Company, Inc.

Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

(*)Fassett, D.W. (1955). Toxicity Report (Unpublished report). Eastman Kodak Company.

Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Eastman Kodak Company.

Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Eastman Kodak Company.

Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Eastman Kodak Company.

Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Eastman Kodak Company.

English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Eastman Kodak Company.

1.0 SUBSTANCE INFORMATION

Generic Name	:	Zinc chloride
Chemical Name	:	Zinc dichloride
CAS Registry No.	:	7646-85-7
Component CAS Nos.	:	
EINECS No.	:	231-592-0
Structural Formula	:	$ZnCl_2$
Additional description	:	
Molecular Weight	:	136.29
Synonyms and Tradenames	:	Zinc (II) chloride; Butter of zinc; zinc butter; RTECS ZH1400000
References	:	ATSDR, 2003 (Agency for Toxic Substances and Disease Registry, Draft Toxicological Profile for Zinc, September 2003)

2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	290 °C
Decomposition	:	
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	2 (reliable with restrictions): Source is well established data compendium.
Reference	:	O'Neil, M.J., Smith, A., Heckelman, P.E., and J.R. Obenchain (eds.). 2002. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Ed. Merck & Co., Inc., Whitehouse Station, NJ.

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	732 °C
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	2 (reliable with restrictions): Source is well established data compendium.
Reference	:	O'Neil, M.J., Smith, A., Heckelman, P.E., and J.R. Obenchain (eds.). 2002. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Ed. Merck & Co., Inc., Whitehouse Station, NJ.

2.3 DENSITY

Type	:	
Guideline/method	:	
Value	:	2.907 at 25°C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	2 (reliable with restrictions): Source is well established data compendium.
Reference	:	O'Neil, M.J., Smith, A., Heckelman, P.E., and J.R. Obenchain (eds.). 2002. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Ed. Merck & Co., Inc., Whitehouse Station, NJ.

2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	
Value	:	
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Expected to be very low based on melting point and boiling point data.
Reliability	:	
Reference	:	

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Not applicable – compound dissociates and ionizes in water
Reliability	:	
Reference	:	

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method	:	
Value	:	4.32 X 10^6 mg/L at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
PKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	2 (reliable with restrictions): Source is well established data compendium.
Reference	:	O'Neil, M.J., Smith, A., Heckelman, P.E., and J.R. Obenchain (eds.). 2002. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Ed. Merck & Co., Inc., Whitehouse Station, NJ.

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	Not flammable
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) :
		epsilon (max) :
		epsilon (295) :
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Halflife (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Not applicable – the metal will not degrade
Reliability	:	
Reference	:	

3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	
Concentration	:	mg/l
Substance measured	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.3.1 TRANSPORT (FUGACITY)

Type	:	
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Year	:	
Test substance	:	

Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :
Kinetic of test subst. : % (specify time and % degradation)
%
%
%
%
Control substance :
Kinetic : %
%
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark : Not applicable – the metal will not degrade
Reliability :
Reference :

3.7 BIOCONCENTRATION

Type :
Guideline/method :
Species :
Exposure period : at °C
Concentration :
BCF :
Elimination :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

4.1 ACUTE TOXICITY TO FISH

Type	:	Acute
Guideline/method	:	Flow-through, freshwater
Species	:	Rainbow trout (*Onchorhynchus mykiss*)
Exposure period	:	96 hr
NOEC	:	
LC0	:	
LC50	:	93 – 0.815 µg Zn/L (depending on juvenile life-stage)
LC100	:	
Limit test	:	
Analytical monitoring	:	No
Year	:	1978
GLP	:	No
Test substance	:	Zinc chloride
Method	:	
Method detail	:	The toxicity of zinc chloride to four juvenile stages of rainbow trout (alvins, swim-up fry, parr, smolts) was determined in 96-h flow-through tests.
Result	:	LC50 values varied by life stage with the swim-up fry being the most sensitive.
Remark	:	The bioavailability and resultant aquatic toxicity of zinc chloride is affected by a variety of factors, including water hardness, pH, dissolved organic carbon and temperature. Reported 96-h LC50 values for zinc chloride (expressed as zinc) for various species of fish include 0.29 mg Zn/L and 0.42 mg Zn/L for bluegill (*Lepomis macrochirus*); 0.093 – 2.17 mg Zn/L for rainbow trout (*Onchorhynchus mykiss*), 0.45 - 2.25 mg Zn/L for common mirror-colored carp (*Cyprinus carpio*) and 1.70 mg Zn/L for sheepshead minnow (*Cyprinodon variegatus*) (U.S. EPA, ECOTOX database, 2003).
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Chapman, G.A. 1978. Toxicities of cadmium, copper, and zinc to four juvenile stages of Chinook and steelheads. Trans. Am. Fish. Soc., 107(6):841-847.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Acute
Guideline/method	:	Flow-through, freshwater
Species	:	*Daphnia magna*
Exposure period	:	48 hr
NOEC	:	
EC0	:	
EC50	:	799 µg Zn/L
EC100	:	
Limit test	:	
Analytical monitoring	:	
Year	:	1982
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Flow-through
Method detail	:	
Result	:	
Remark	:	The bioavailability and resultant aquatic toxicity of zinc chloride is affected by a variety of factors, including water hardness, pH, dissolved organic carbon and temperature. Reported 48-h EC50 values for zinc chloride (expressed as zinc) for *Daphnia magna* include 0.33, 0.52, 0.66 and 0.80

		mg Zn/L (U.S. EPA, ECOTOX database, 2003). For several crustaceans, including *Daphnia magna*, *Ceriodaphnia dubia*, and *Ceriodaphnia reticulata*, reported 48-h EC50 values ranged from 0.068 to 0.86 mg Zn/L, for zinc tested as zinc chloride or zinc sulfate.
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Attar, E.N. and E.J. Maly. 1982. Acute toxicity of cadmium, zinc, and cadmium-zinc mixtures to *Daphnia magna*. Arch. Environ. Contam. Toxicol., 11(3):291-296.

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	:	Algal growth assay
Guideline/method	:	Static
Species	:	*Selenastrum capricornutum*
Endpoint	:	Growth
Exposure period	:	96 hr
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	44.7 µg Zn/L
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Microplate algal assay
Method detail	:	
Result	:	
Remark	:	The bioavailability and resultant aquatic toxicity of zinc is affected by a variety of factors, including water hardness, pH, dissolved organic carbon and temperature The reported 72-h EC50 for the marine diatom *Skeletonema costatum* was 0.142 mg Zn/L (U.S. EPA, ECOTOX database, 2003).
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Alaise, C., R. Legault, N. Bermingham, R. Van Coillie, and P. Vasseur. 1986. A simple microplate algal assay technique for aquatic toxicity assessment. Toxic. Assess., 1:261-281.

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st.: 2nd.: 3rd.:
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Zinc is an essential element in nutrition, and is important in membrane stability, in over 300 enzymes, and in the metabolism of proteins and acids. (WHO, 2001, Environmental Health Criteria 221, Zinc). Absorption of zinc in laboratory animals can vary from 10-40% depending upon nutritional status and other ligands in the diet. Absorbed zinc is mainly deposited in muscle, bone, liver, pancreas, kidney and other organs. The biological half-life of zinc ranges from 4 to 50 days in rats depending on the administered dose (WHO, 2001, Environmental Health Criteria 221, Zinc). Increases in zinc concentration in the bodies of experimental animals exposed to zinc are accompanied by reduced levels of copper, suggesting that some of the signs of toxicity ascribed to zinc may be caused by zinc-induced copper deficiency. Moreover, studies have shown that exposure to zinc alters the levels of other essential metals, including iron. Zinc deficiency in animals is characterized by a reduction in growth and cell replication, adverse reproductive and developmental effects, and reduced immunoresponsiveness. (WHO, 2001, Environmental Health Criteria 221, Zinc).
Reliability	:	
Reference	:	

5.1.1 ACUTE ORAL TOXICITY

Type	:	Oral
Guideline	:	Not specified
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Male
Number of animals	:	10 per dose group
Vehicle	:	Water
Doses	:	Not specified
LD50	:	1,100 mg/kg b.w. as $ZnCl_2$ (95% C.I. = 661 – 1,830 mg/kg b.w.) 528 mg/kg b.w. as zinc (95% C.I. = 316 – 875 mg/kg b.w.)
Year	:	1988
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Single doses administered intragastrically.
Method detail	:	Rats weighed 230 – 280 g. Solution concentrations were adjusted so that a 300–g rat received a 1 ml dose. Solutions were adjusted to a pH of between 6.0 and 7.0, using sodium biocarbonate when necessary.
Result	:	Acute LD50 values of zinc chloride were also determined using i.p administration in this study. The toxicity of zinc chloride to rats was much greater after i.p. administration with an LD50 of 58 mg/kg b.w. when expressed as $ZnCl_2$ (95% C.I. = 43 – 79) or 28 mg/kg b.w. when expressed as zinc (95% C.I. = 21 – 38). The much lower toxicity by the oral route of administration suggests a low rate of absorption of zinc chloride from the gastrointestinal tract.
Remark	:	Acute oral toxicity in rodents exposed to zinc compounds is low, and the level at which zinc produces no adverse effect in rats is approximately 160 mg/kg body weight (WHO, 2001, Environmental Health Criteria 221, Zinc). Of the compounds zinc nitrate, zinc sulfate, zinc chloride and zinc acetate, zinc acetate was the most toxic, with oral LD50 values of 237 mg Zn/kg bw (rat) and 86 mg Zn/kg bw (mouse).
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Domingo, J.L., J.M. Llobet, J.l. Paternain, and J. Corbella. 1988. Acute zinc intoxication: comparison of the antidotal efficacy of several chelating agents. Vet. Hum. Toxicol., 30(3): 224-228.

Type	:	Oral
Guideline/Method	:	Not specified
Species	:	Mouse
Strain	:	Swiss
Sex	:	Male
Number of animals	:	10 per dose group
Vehicle	:	Water
Doses	:	Not specified
LD50	:	1,260 mg/kg b.w. as $ZnCl_2$ (95% C.I. = 775 – 2,300 mg/kg b.w.) 605 mg/kg b.w. as zinc (95% C.I. = 370 – 1,099 mg/kg b.w.)
Year	:	1988
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Single doses administered intragastrically.
Method detail	:	Mice weighed 24 – 28 g. Solution concentrations were adjusted so that a 30–g mouse received a 0.21 ml dose. Solutions were adjusted to a pH of between 6.0 and 7.0, using sodium biocarbonate when necessary.
Result	:	Acute LD50 values of zinc chloride were also determined using i.p administration in this study. The toxicity of zinc chloride to mice was much greater after i.p. administration with an LD50 of 91 mg/kg b.w. when

		expressed as $ZnCl_2$ (95% C.I. = 57 – 146) or 44 mg/kg b.w. when expressed as zinc (95% C.I. = 27 – 69). The much lower toxicity by the oral route of administration suggests a low rate of absorption of zinc chloride from the gastrointestinal tract.
Remark	:	
Reliability	:	2, reliable with restrictions: Comparable to guideline study with adequate documentation.
Reference	:	Domingo, J.L., J.M. Llobet, J.l. Paternain, and J. Corbella. 1988. Acute zinc intoxication: comparison of the antidotal efficacy of several chelating agents. Vet. Hum. Toxicol., 30(3): 224-228.

5.1.2 ACUTE INHALATION TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Concentrations	:	
Exposure time	:	
LC50	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Zinc chloride is a primary ingredient in smoke bombs, resulting in respiratory injury. In a 10-minute inhalation study with rats, zinc chloride aerosol was lethal at concentrations as low as 940 mg Zn/m^3 (Risk Assessment for Zinc Metal, 2001, draft).
Reliability	:	
Reference	:	

5.1.3 ACUTE DERMAL TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
LD50	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Zinc chloride is reported to cause moderate to severe skin irritation in the rabbit, guinea pig and mouse at 0.48 mg Zn/cm2 while zinc acetate at 7.2

		mg Zn/cm^2 was reported to be irritating to the rabbit and mouse but caused no effects in the guinea pig (ATSDR, 1994, Toxicological Profile for Zinc).
Reliability	:	
Reference	:	

5.2.1 SKIN IRRITATION

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Zinc chloride, applied daily as a 1% aqueous solution in an open patch test for 5 days, was severely irritant in rabbits, guinea pigs and mice, inducing epidermal hyperplasia and ulceration. (Lansdown, 1991 as cited in WHO, 2001, Environmental Health Criteria 221, Zinc).
Reliability	:	
Reference	:	

5.2.2 EYE IRRITATION

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

5.4 REPEATED DOSE TOXICITY

Type	:	28-d Oral
Guideline	:	Not specified
Species	:	Rat
Strain	:	Wistar
Sex	:	Both male and female
Number of animals	:	13 males; 17 females in treatment group
Route of admin.	:	Drinking water
Exposure period	:	4 weeks
Frequency of treatment	:	Continuous
Post exposure period	:	None
Doses	:	11.66 mg Zn/kg b.w./day in males and 12.75 mg Zn/kg b.w./day in females on average from 0.12 mg Zn/cm^3 in water
Control group	:	Yes
NOAEL	:	None
LOAEL	:	12 mg Zn/kg b.w./day
Other	:	
Year	:	1992
GLP	:	No
Test substance	:	Zinc chloride
Method	:	
Method detail	:	Two-month-old Wistar rats of both sexes received zinc chloride in their drinking water for a period of 4 weeks. Liquid consumption was monitored so that the average daily Zn exposure could be calculated. At study termination, rats were weighed, bled, and sacrificed. Hematological indices were determined on blood samples.
Result	:	Zinc treatment had no effect on the survival or body weight gain of exposed rats. Zinc treatment also had no appreciable affect on the composition of bone marrow cells. However, erythrocytes counts and hemoglobin levels in the peripheral blood were significantly decreased in Zn-exposed males and females compared to controls, while the numbers of leukocytes, neutrophils, and lymphocytes in male rats were increased compared to controls.
Remark	:	Long-term oral exposure to zinc compounds indicates the target organs of toxicity to be the hematopoeitic system in rats, ferrets and rabbits; the kidney in rats and ferrets; and the pancreas in mice and ferrets (WHO, 2001, Environmental Health Criteria 221, Zinc). Zinc acetate given to rats in water over three months yielded NOAEL values of 95 to 191 mg Zn/kg/d. During a 13-week exposure to zinc sulfate via the diet, NOAEL values for the rat ranged from 53 to 565 mg Zn/kg/day and for the mouse were 104 mg Zn/kg/d, based upon various parameters. (ATSDR, 2003, Draft Toxicological Profile for Zinc).
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Zaporowska, H. and W. Wasilewski. 1992. Combined effect of vanadium and zinc on certain selected haematological indices in rats. Comp. Biochem. Physiol., 103C: 143-147.

Type	:	13-week Oral
Guideline/method	:	Not specified
Species	:	Rat
Strain	:	Wistar
Sex	:	Male and female
Number of animals	:	12 of each sex per treatment group
Route of admin.	:	Diet
Exposure period	:	13 wk
Frequency of treatment	:	Continuous

Post exposure period	:	None
Doses	:	0, 300, 3,000, or 30,000 ppm in diet (equivalent to an average daily intake of 23.2, 234, or 2,514 mg $ZnSO_4$/kg/d in males and 24.5, 243, or 2,486 mg $ZnSO_4$/kg/d in females
Control group	:	Yes, for both males and females
NOAEL	:	3,000 ppm in diet (equivalent to approximately 234 mg $ZnSO_4$/kg/d in males and 243 mg $ZnSO_4$/kg/d in females)
LOAEL	:	30,000 ppm in diet (equivalent to approximately 2,514 mg $ZnSO_4$/kg/d in males and 2,486 mg $ZnSO_4$/kg/d in females)
Other	:	
Year	:	1981
GLP	:	No
Test substance	:	$ZnSO_4 \bullet 7H_2O$
Method	:	
Method detail	:	Groups of male and female rats (12 each) were feed diets containing zinc sulfate for 13 weeks. Animals were observed daily for clinical signs of toxicity and weighed weekly. Feed and water intake was measured twice per week. Prior to study termination, blood samples were collected and analyzed for hematological and biochemical parameters. Following necropsy, gross pathological and histopathological examinations were conducted on selected target organs and tissues. Organs weights were also determined.
Results	:	No compound-related mortality was observed at any dose level. The only clinical signs of toxicity were behavioral (removal of chow from the feeding container) and confined to the highest feeding level (30,000 ppm). At the highest dose level, food consumption, water intake and growth were reduced, particularly in males. A moderate reduction in the total leukocyte count was observed in both sexes in the high dose groups, whereas males in this group also showed slightly decreased hematocrit and hemoglobin levels. GOT and GPT concentrations were decreased in all male groups but there was no dose-response trend. Total protein, cholesterol and calcium in the blood were decreased in high dose males, whereas only calcium was elevated in high dose females. Necropsy results indicated no remarkable gross lesions in rats at any dose level, although the weights (both absolute and relative) of the livers and kidneys of the males in the 30,00 ppm group showed a slight to moderate decrease. Histopathological examinations showed pancreatic lesions attributable to treatment in the high dose groups. Lesions consisted of degeneration and necrosis of the acinar cells, clarification of centroacinar cells, and interstitial fibrosis.
Remark	:	While not conducted on the zinc chloride salt, the results of this study on hydrated zinc sulfate are considered relevant for assessing the potential hazard of the chloride because both salts are soluble and expected to have a similar bioavailability and toxicity. In general, after oral or dermal exposure, the toxicities of all zinc compounds are comparable (ATSDR, 2003. Draft Toxicological Profile for Zinc).
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Maita, K., M. Hirano, K. Mitsumori, K. Takahashi, and Y. Shirasu. 1981. Subacute toxicity studies with zinc sulfate in mice and rats. J. Pesticide Sci., 6: 327-336.
Type	:	13-week Oral
Guideline/method	:	Not specified
Species	:	Mouse
Strain	:	ICR (specific pathogen-free)
Sex	:	Male and female
Number of animals	:	12 of each sex per treatment group

Route of admin.	:	Diet
Exposure period	:	13 wk
Frequency of treatment	:	Continuous
Post exposure period	:	None
Doses	:	0, 300, 3,000, or 30,000 ppm in diet (equivalent to an average daily intake of 42.7, 458, or 4,927 mg $ZnSO_4$/kg/d in males and 46.4, 479, or 4,878 mg $ZnSO_4$/kg/d in females
Control group	:	Yes, for both males and females
NOAEL	:	3,000 ppm in diet (equivalent to approximately 458 mg $ZnSO_4$/kg/d in males and 479 mg $ZnSO_4$/kg/d in females)
LOAEL	:	30,000 ppm in diet (equivalent to approximately 4,927 mg $ZnSO_4$/kg/d in males and 4,878 mg $ZnSO_4$/kg/d in females)
Other	:	
Year	:	1981
GLP	:	No
Test substance	:	$ZnSO_4 \bullet 7H_2O$
Method	:	
Method detail	:	Groups of male and female mice (12 each) were feed diets containing zinc sulfate for 13 weeks. Animals were observed daily for clinical signs of toxicity and weighed weekly. Feed and water intake was measured twice per week. Prior to study termination, blood samples were collected and analyzed for hematological and biochemical parameters. Following necropsy, gross pathological and histopathological examinations were conducted on selected target organs and tissues. Organs weights were also determined.
Results	:	Although there were no obvious clinical signs of toxicity, four of 12 males in the high dose (30,000 ppm) group died or were killed *in extremis*. One female fed at this level also died. Histological findings in these animals revealed impairment of the urinary tract and regressive changes in the exocrine gland of the pancreas. Food consumption, water intake, and growth were depressed in the high dose groups, with the greatest effects seen in males. Male and female mice in the 30,000 ppm group showed moderately reduced levels of hematocrit and hemoglobin compared to controls; the leukocyte counts in these males were also decreased moderately. Mice of both sexes in the high dose groups showed a slight to moderate decrease in total protein, glucose and cholesterol, and a moderate to marked increase in alkaline phosphatase and urea nitrogen. Additional findings included depressed GPT levels in females, increased blood calcium levels in females, and increased GOT levels in males. Gross pathological changes in the high-dose animals included marked emaciation, ischemic discoloration of the kidney and thyroid, atrophy of the pancreas, edematous thickening of the upper small intestine, slight splenomegaly, and ulcers of the fore-stomach. Histopathological lesions were observed in the pancreas (swollen nuclei, necrosis of acinar cells), upper intestine (proliferation of epithelial cells), fore-stomach (ulcerations), spleen (proliferation of erythropoietic immature cells), and kidney (regression of renal cortex in females).
Remark	:	Results were consistent with those in rats (see previous robust summary); however, the effects on mice were generally more severe at the same level (ppm) in the diet. Most likely this was due to the much higher dose levels of zinc sulfate in mice compared to rats (approximately double on a mg/kg/d basis) due to their smaller size and greater relative food intake.
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Maita, K., M. Hirano, K. Mitsumori, K. Takahashi, and Y. Shirasu. 1981. Subacute toxicity studies with zinc sulfate in mice and rats. . J. Pesticide Sci., 6: 327-336.

5.5 GENETIC TOXICITY - MUTAGENICITY

Type	:	Mutagenicity
Guideline/method	:	Rec-assay
System of testing	:	Bacteria *in vitro*
Species	:	*Bacillus subtilis*
Strain	:	H17 (rec+) and M45 (rec-)
Test concentrations	:	0.05 M
Cytotoxic concentr.	:	Not determined
Metabolic activation	:	No
Year	:	1975
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Kada et al., 1972. Mutation Res., 16:165-174.
Method detail	:	An 0.05 ml aliquot of a 0.05 M zinc chloride solution was tested.
Result	:	At the concentration tested, there was no inhibition of either the rec+ or rec- strain of *Bacillus subtilis*, suggesting that zinc chloride did not cause DNA damage.
Remark	:	In 11 separate in vitro studies with zinc chloride or zinc sulfate, negative results were reported with the exception of two ambiguous results and one weakly positive result. (Risk Assessment for Zinc Metal, 2001, draft). Genotoxicity studies in a variety of test systems have failed to provide evidence for mutagenicity of zinc. However, there are indications of weak clastogenicity following zinc exposure (ATSDR, 2003 Draft Toxicological Profile for Zinc). The results of short-term genotoxicity assays for zinc are equivocal. Responses in mutagenicity assays are thought to depend on the form (e.g., inorganic or organic salt) of the zinc tested (U.S. EPA, 2003, Integrated Risk Information System (IRIS) Summary for Zinc and Compounds).
Reliability	:	2 (reliable with restrictions): Acceptable study with adequate documentation.
Reference	:	Nisioka, H. 1975. Mutagenic activities of metal compounds in bacteria. Mutation Res., 31: 185-189.

Type	:	Mutagenicity
Guideline/method	:	Microscreen assay
System of testing	:	Bacteria *in vitro*
Species	:	*Escherichia coli*
Strain	:	$WP_s(\lambda)$
Test concentrations	:	Not specified
Cytotoxic concentr.	:	>1 mM
Metabolic activation	:	No
Year	:	1987
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Rossman et al., 1984. Environ. Mut., 6:59.
Method detail	:	
Result	:	Negative for Trp+ reversion, λ Prophage induction and WP2 comutagenenesis
Remark	:	
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Rossman, T.G., J.T. Zelikoff, S. Agarwal, and T.J. Kneip. 1987. Genetic toxicology of metal compounds: an examination of appropriate cellular

models. Toxicol. Environ. Chem., 14:251-262.

Type	:	Mutagenicity
Guideline/method	:	L5178Y/TK somatic cell point mutation assay
System of testing	:	Cultured mouse lymphoma cells – *in vitro*
Species	:	Mouse
Strain	:	L5178/TK$^{+/-}$
Test concentrations	:	1.21 – 12.13 μg/ml
Cytotoxic concentr.	:	Not determined
Metabolic activation	:	No
Year	:	1980
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Clive et al., 1972. Mutation Res., 16:77-87.
Method detail	:	
Result	:	Zinc chloride was not mutagenic under the test conditions.
Remark	:	
Reliability	:	2 (reliable with restrictions): Acceptable study with adequate documentation.
Reference	:	Amacher, D.E. and S.C. Paillet. 1980. Induction of trifluorothymidine-resistant mutants by metal ions in L5178Y/TK+/- cells. Mutation Res., 78: 279-288.

5.6 GENETIC TOXICITY - CLASTOGENICITY

Type	:	Chromosomal aberrations in bone marrow cells
Guideline/method	:	*In vivo*
Species	:	Mouse
Strain	:	C57B1
Sex	:	Male
Route of admin.	:	Diet
Exposure period	:	One month
Doses	:	0.5% Zn in feed
Year	:	1979
GLP	:	No
Test substance	:	Zinc chloride
Method	:	
Method detail	:	8-week-old mice kept on a normal (1.1% calcium) or low-calcium (0.03%) diet were exposed for one month to zinc chloride (0.5% Zn). After test termination, the bone marrow cells (50 metaphases/animal) from 10 animals were assayed for chromosomal aberrations.
Result	:	The body weights of mice fed zinc in the diet, either with normal or low calcium, were significantly reduced compared to their respective controls. Zinc treatment caused a significant increase in cells with structural aberrations (primarily dicentric chromosomes) for mice on low calcium diets. Aberrations were also increased in Zn-treated mice with normal calcium diets, but the increase was not statistically significant.
Remark	:	Studies on the induction of chromosome aberrations in bone marrow cells harvested from animals exposed to zinc compounds have yielded equivocal results. Increased aberrations have been seen in rats after oral exposure to zinc chloride in water (249 mg/L for 14 days) and in mice given intraperitoneal injections of zinc chloride (2-5 mg/kg as zinc chloride). In contrast, other studies have produced negative findings or have suggested that the induction of aberrations is contingent upon concomitant calcium deficiency. Negative results have been reported in the mouse micronucleus test (i.p. injection of zinc sulfate) and in the dominant lethal mutation assay

with mice (i.p. injection of zinc chloride at 15 mg/kg). (WHO, 2001, Environmental Health Criteria 221, Zinc).

Reliability : 2 (reliable with restrictions): Acceptable study with adequate documentation.

Reference : G. Deknudt and G.B. Gerber. 1979. chromosomal aberrations in bone-marrow cells of mice given a normal or a calcium-deficient diet supplemented with various heavy metals. Mutation Res., 68:163-168.

5.8.2 DEVELOPMENTAL TOXICITY

Type	:	Teratogenicity
Guideline	:	Not specified
Species	:	Mouse
Strain	:	CF-1 albino
Sex	:	Female
Route of admin.	:	Intraperitoneal
Exposure period	:	Day 8, 9, 10, or 11 of gestation
Frequency of treatment	:	Single dose
Duration of test	:	To gestation Day 18
Doses	:	12.5, 20.5, or 25 mg $ZnCl_2$/kg
Control group	:	Yes (distilled water only)
NOAEL maternal tox.	:	12.5 mg $ZnCl_2$/kg
NOAEL teratogen.	:	12.5 mg $ZnCl_2$/kg
Other	:	
Other	:	
Other	:	
Year	:	1977
GLP	:	No
Test substance	:	Zinc chloride
Method	:	
Method detail	:	Gravid female mice were given an i.p. injection of either 12.5, 20.5 or 25 mg $ZnCl_2$/kg on Day 8, 9, 10, or 11 of gestation. Following the respective treatments, the mice were allowed to continue their gestation uninterrupted until Day 18 (one day prior to expected delivery), when each pregnant mouse was sacrificed. The number of fetuses and resorption sites (metrial glands) was determined and recorded. Each fetus was then weighed, sexed, and examined for external defects. Every other fetus was processed for skeletal examination by the method of Staples and Schnell (1964).
Result	:	Zinc chloride, when administered in doses of 20.5 and 25 mg/kg, produced significant incidences of skeletal defects in fetuses as compared to those observed in the water-treated group on Day 11. Both doses also resulted in mortality of gravid females. The majority of defects involved the rib cage and included a ripple rib anomaly; however, the zinc salt failed to produce a significant incidence of soft tissue anomalies with either treatment regimen. As the dosage of $ZnCl_2$ was reduced, maternal and fetal toxicity, relative fetal weights, and the incidences of skeletal anomalies were correspondingly decreased. Maternal toxicity and incidences of skeletal anomalies were greatest when doses were administered on Day 11 of gestation. Zinc chloride, given at 12.5 mg/kg on day 11 of gestation, induced nonsignificant incidences of both skeletal and soft tissue defects compared to controls. No deaths were observed in the gravid females and no ripple ribs were observed in their fetuses.
Remark	:	Developmental toxicity data for several zinc compounds are available. Second-generation mice (from mothers fed zinc carbonate) exposed to high doses of zinc throughout the gestation, lactation, and postweaning periods had elevated levels of zinc in their bones, decreased blood copper levels, lowered hematocrit values and reduced body weights. The offspring of

pregnant rats fed zinc carbonate (500 mg Zn/kg) did not demonstrate any increase in the incidence of malformations. (WHO, 2001, Environmental Health Criteria 221, Zinc). Several developmental toxicity studies have been conducted with zinc sulfate on mice, rats, hamsters and rabbits, in general accordance with OECD Guideline 414; however, the form of the zinc sulfate was not specified. Depending upon the form that was used, the calculated NOAEL values ranged from 6.8 mg Zn/kg bw for the mouse to 35.2 mg Zn/kg bw for the hamster. (Risk Assessment for Zinc Metal, 2001, draft).

Reliability : 2 (reliable with restrictions): Comparable to guideline study with adequate documentation.

Reference : Chang, C-H., D.E. Mann, and R.F. Gautieri. 1977. Teratogenicity of zinc chloride, 1,10-phenanthroline, and a zinc-1,10-phenanthroline complex in mice. J. Pharm. Sci., 66:1755-1758.

5.8.3 TOXICITY TO REPRODUCTION

Type	:	Single-generation pilot breeding study
Guideline	:	Not specified
In vitro/in vivo	:	In vivo
Species	:	Rat
Strain	:	Sprague-Dawley SDTM
Sex	:	Both male and female
Route of admin.	:	Oral gavage
Exposure period	:	Males: Prior to cohabitation (77 d) and during cohabitation (21 d) Females: Prior to cohabitation (77 d), during cohabitation (21 d), and throughout gestation (21 d) and lactation (21 d).
Frequency of treatment	:	7 days/week
Duration of test	:	140 days (20 wk)
Doses	:	0, 7.5, 15, and 30 mg $ZnCl_2$/kg/d
Control group	:	Yes
Year	:	2001
GLP	:	No
Test substance	:	Zinc chloride
Method	:	Single generation breeding study
Method detail	:	Male and female rats (10 each per treatment) were administered 0.0, 7.5, 15.0, or 30.0 $ZnCl_2$ for 77 days prior to mating. At the end of the pre-mating period, males and females were paired within the same dose groups. Dosing was continued for both sexes throughout mating. All males were euthanized at the conclusion of mating, weighed, necropsied, and examined for morphological changes. Dosing was continued for females throughout gestation and lactation. Pregnant females were allowed to deliver their offspring naturally. Litter sizes were standardized on day 4 after birth to 4 of each sex. At day 21 of lactation, all F_0 females were sacrificed, necropsied, and examined for morphological changes. The evaluation of reproductive performance included fertility, viability index, weaning index, litter size, and the body weight of pups on days 0, 4, 7, 14, and 21 of lactation.
Results	:	The fertility indices in all dose groups were significantly lower than in the control group, but did not show a dose-response relationship. Pup viability indices on days 0 and 4 for the high-dose group were significantly lower than those of the control group. The body weights of pups in the highest dose group on days 14 and 21 were significantly lower than those in the control group. There were no effects on weaning indices or sex ratios. Overall, the results suggested that $ZnCl_2$ has only mild effects on rat reproductive performance up to 30 mg/kg/d. In addition, there were no significant treatment-related changes observed in any of the clinical

		pathology parameters that were evaluated. All histopathologic effects related to treatment were mild. Those in the reproductive organs were confined to males only and according to the authors probably precluded any adverse effects upon reproduction.
Remark	:	The effects on reproduction of other zinc compounds have also been studied. The LOAEL for serious reproductive effects in female rats was 200 and 250 mg Zn/kg/d from exposure to zinc sulfate and zinc carbonate, respectively, in the diet. (ATSDR, 2003, Draft Toxicological Profile for Zinc).
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Khan, A.T., A. Atkinson, T.C. Graham, M. Green, S. Ali, S.J. Thompson, and K.F. Shireen. 2001. Effects of low levels of zinc on reproductive performance of rats. Environ. Sci. (Tokyo), 8(4): 367-381.

Type	:	Sperm chromatin structure
Guideline	:	None
In vitro/in vivo	:	In vivo
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Male
Route of admin.	:	Diet
Exposure period	:	8 weeks
Frequency of treatment	:	Continuous
Duration of test	:	8 weeks
Doses	:	4, 12, or 500 mg Zn/kg of diet (ppm)
Control group	:	No
Year	:	1993
GLP	:	No
Test substance	:	Zinc chloride
Method	:	
Method detail	:	Three-week old male rats (10 per group) were fed experimental diets with concentrations of zinc considered to be deficient (4 mg/kg), adequate (12 mg/kg) or excessive (500 mg/kg). After 8 weeks of feeding, animals were sacrificed to obtain testicular germ cells and epididymal sperm. Flow-cytometric procedures were used to determine effects on rat testicular development, including integrity of caudal epididymal sperm chromatin structure defined as the susceptibility of DNA to denaturation *in situ*.
Results	:	Rats fed the zinc deficient (4 ppm) diet demonstrated significant deviations in the ratio of testicular cell types present, including a reduction of S phase and total haploid cells. In addition, approximately 50% of epididymal sperm has a significant decrease in resistance to DNA denaturation *in situ*. Rats fed either a Zn-adequate or Zn-excess diet did not demonstrate an abnormal testicular cell type ratio. Excess Zn had a negative effect on chromatin structure, but much less than that of Zn deficiency.
Remark	:	Rats fed zinc chloride daily over an 8 week period demonstrated altered sperm chromatin structure with a LOAEL of 25 mg Zn/kg/d.
Reliability	:	2 (reliable with restrictions): Comparable to guideline study with adequate documentation.
Reference	:	Evenson, D.P., R.J. Emerick, L.K. Jost, H. Kayongo-Male, and S.R. Stewart. 1993. Zinc-silicon interactions influencing sperm chromatin integrity and testicular cell development in the rat as measured by flow cytometry. J. Anim. Sci., 71:955-962.

6.0 OTHER INFORMATION

6.1 Carcinogenicity

No adequate experimental evidence has been found to indicate that zinc salts administered orally or parenterally are tumorigenic. (WHO, 2001, Environmental Health Criteria 221, Zinc).